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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09  CA/CAplus records now contain indexing from 1907 to the
                  present
 NEWS  4  DEC 08  INPADOC: Legal Status data reloaded
 NEWS  5  SEP 29  DISSABS now available on STN
 NEWS  6  OCT 10  PCTFULL: Two new display fields added
 NEWS  7  OCT 21  BIOSIS file reloaded and enhanced
 NEWS  8  OCT 28  BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS  9  NOV 24  MSDS-CCOHS file reloaded
 NEWS 10  DEC 08  CABA reloaded with left truncation
 NEWS 11  DEC 08  IMS file names changed
 NEWS 12  DEC 09  Experimental property data collected by CAS now available
                  in REGISTRY
 NEWS 13  DEC 09  STN Entry Date available for display in REGISTRY and CA/CAplus
 NEWS 14  DEC 17  DGENE: Two new display fields added
 NEWS 15  DEC 18  BIOTECHNO no longer updated
 NEWS 16  DEC 19  CROPU no longer updated; subscriber discount no longer
                  available
 NEWS 17  DEC 22  Additional INPI reactions and pre-1907 documents added to CAS
                  databases
 NEWS 18  DEC 22  IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
 NEWS 19  DEC 22  ABI-INFORM now available on STN
 NEWS 20  JAN 27  Source of Registration (SR) information in REGISTRY updated
                  and searchable
 NEWS 21  JAN 27  A new search aid, the Company Name Thesaurus, available in
                  CA/CAplus
 NEWS 22  FEB 05  German (DE) application and patent publication number format
                  changes

 NEWS EXPRESS  DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
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FILE 'HOME' ENTERED AT 12:54:31 ON 19 FEB 2004

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FILE 'USPATFULL' ENTERED AT 12:57:56 ON 19 FEB 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 19 Feb 2004 (20040219/PD)
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FILE LAST UPDATED: 19 Feb 2004 (20040219/ED)
HIGHEST GRANTED PATENT NUMBER: US6694518
HIGHEST APPLICATION PUBLICATION NUMBER: US2004034897
CA INDEXING IS CURRENT THROUGH 19 Feb 2004 (20040219/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 19 Feb 2004 (20040219/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2003

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substance identification.

=> e lenhard james m/in
E1 7 LENHARD FRIEDRICH/IN
E2 1 LENHARD HOLGER/IN
E3 0 --> LENHARD JAMES M/IN
E4 3 LENHARD JAMES MARTIN/IN
E5 14 LENHARD JEROME R/IN
E6 1 LENHARD LUBESEDER ULRICH/IN
E7 1 LENHARD M JAMES/IN
E8 2 LENHARD MARTIN/IN
E9 1 LENHARD MICHAEL/IN
E10 8 LENHARD MYRON J/IN
E11 2 LENHARD MYRON JAMES/IN
E12 1 LENHARD PETER/IN

=> s e4
L1 3 "LENHARD JAMES MARTIN"/IN

=> d l1,cbib,ab,1-3

L1 ANSWER 1 OF 3 USPATFULL on STN
2003:238420 COMBINATIONS OD DIPEPTIDYL PEPTIDASE IV INHIBITORS AND OTHER
ANTIDIABETIC AGENTS FOR THE TREATMENT OF DIABETES MELLITUS.
Arch, Jonathan Robert Sanders, Essex, UNITED KINGDOM
Lenhard, James Martin, Durham, NC, UNITED STATES
US 2003166578 A1 20030904
APPLICATION: US 2003-311446 A1 20030220 (10)
WO 2001-GB2696 20010619
PRIORITY: GB 2000-14969 20000619
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal such as a human, which method comprises administering an effective, non-toxic and pharmaceutically acceptable amount of a dipeptidyl peptidase IV inhibitor and another antidiabetic agent, to a mammal in

need thereof.

L1 ANSWER 2 OF 3 USPATFULL on STN
2003:89397 Thiazole derivatives as PPAR gamma ligands.
Collins, Jon Loren, Durham, NC, United States
Holmes, Christopher Patrick, Saratoga, CA, United States
Lenhard, James Martin, Raleigh, NC, United States
Willson, Timothy Mark, Durham, NC, United States
SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
US 6541492 B1 20030401
WO 2000027832 20000518
APPLICATION: US 2001-831672 20010511 (9)
WO 1999-EP8477 19991109
PRIORITY: GB 1999-98246143 19991108
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention discloses novel PPAR gamma ligands of Formula (I) and pharmaceutically acceptable salts and solvates thereof. The present invention also discloses a method for treating osteoporosis by administration of a PPAR gamma antagonist.

L1 ANSWER 3 OF 3 USPATFULL on STN
2002:273441 PPAR gamma ligands.
Collins, Jon Loren, Durham, NC, UNITED STATES
Holmes, Christopher Patrick, Saratoga, CA, UNITED STATES
Lenhard, James Martin, Raleigh, NC, UNITED STATES
Willson, Timothy Mark, Durham, NC, UNITED STATES
US 2002151569 A1 20021017
APPLICATION: US 2002-115550 A1 20020403 (10)
PRIORITY: GB 1998-246143 19981111
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention discloses a method for treating osteoporosis by administration of a PPAR gamma antagonist.

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FILE 'USPATFULL' ENTERED AT 12:57:56 ON 19 FEB 2004
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L1 3 S E4

=> s (lipodystrophy or dyslipidemia or fat redistribution or hyperlipidemia)
157 LIPODYSTROPHY
836 DYSLIPIDEMIA
57034 FAT
11165 REDISTRIBUTION
15 FAT REDISTRIBUTION
(FAT(W)REDISTRIBUTION)
3626 HYPERLIPIDEMIA
L2 4172 (LIPODYSTROPHY OR DYSLIPIDEMIA OR FAT REDISTRIBUTION OR HYPERLIPIDEMIA)

=> s l2 and (retrovir? or HIV or human immunodeficiency virus or HTLV? or human t-cell leukemia
28929 RETROVIR?
29336 HIV
372979 HUMAN
16965 IMMUNODEFICIENCY
70100 VIRUS
12163 HUMAN IMMUNODEFICIENCY VIRUS
(HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
5725 HTLV?
372979 HUMAN

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         453882 CELL
          27731 LEUKEMIA
          70100 VIRUS
            935 HUMAN T-CELL LEUKEMIA VIRUS
                  (HUMAN(W)T(W)CELL(W)LEUKEMIA(W)VIRUS)
L3          894 L2 AND (RETROVIR? OR HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR
                HTLV? OR HUMAN T-CELL LEUKEMIA VIRUS)

=> s l3 and (lipodystrophy or dyslipidemia)
            157 LIPODYSTROPHY
            836 DYSLIPIDEMIA
L4          334 L3 AND (LIPODYSTROPHY OR DYSLIPIDEMIA)

=> s l4 and (antiviral? or HAART or highly active antiretroviral therapy)
          19009 ANTIVIRAL?
            157 HAART
         767004 HIGHLY
         721523 ACTIVE
           1215 ANTIRETROVIRAL
         109568 THERAPY
             96 HIGHLY ACTIVE ANTIRETROVIRAL THERAPY
                  (HIGHLY(W)ACTIVE(W)ANTIRETROVIRAL(W)THERAPY)
L5          153 L4 AND (ANTIVIRAL? OR HAART OR HIGHLY ACTIVE ANTIRETROVIRAL
                THERAPY)

=> s l5 and (lipodystrophy/clm or dyslipidemia/clm or hyperlipidemia/clm or fat redistribution/
             22 LIPODYSTROPHY/CLM
            203 DYSLIPIDEMIA/CLM
            664 HYPERLIPIDEMIA/CLM
           8720 FAT/CLM
            877 REDISTRIBUTION/CLM
              0 FAT REDISTRIBUTION/CLM
                  ((FAT(W)REDISTRIBUTION)/CLM)
L6           12 L5 AND (LIPODYSTROPHY/CLM OR DYSLIPIDEMIA/CLM OR HYPERLIPIDEMIA/
                CLM OR FAT REDISTRIBUTION/CLM)

=> d l6,cbib,ab,1-12

L6   ANSWER 1 OF 12  USPATFULL on STN
2004:44514 Polynucleotides encoding novel human mitochondrial and microsomal
    glycerol-3-phosphate acyl-transferases and variants thereof.
    Farrelly, Dennis, Monmouth Junction, NJ, UNITED STATES
    Chen, Jian, Princeton, NJ, UNITED STATES
    Nelson, Thomas C., Lawrenceville, NJ, UNITED STATES
    Feder, John N., Belle Mead, NJ, UNITED STATES
    Wu, Shujian, Langhorne, PA, UNITED STATES
    Bassolino, Donna A., Hamilton, NJ, UNITED STATES
    Krystek, Stanley R., Ringoes, NJ, UNITED STATES
    US 2004033506 A1 20040219
    APPLICATION: US 2002-308128  A1  20021202 (10)
    PRIORITY: US 2001-334904P  20011130 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
AB      The present invention provides novel polynucleotides encoding
        Mitochondrial GPAT, Microsomal GPAT_hlog1, Microsomal GPAT_hlog2,
        Microsomal GPAT_hlog3, and/or Microsomal GPAT_hlog3_v1 polypeptides,
        fragments and homologues thereof. Also provided are vectors, host cells,
        antibodies, and recombinant and synthetic methods for producing said
        polypeptides. The invention further relates to diagnostic and
        therapeutic methods for applying these novel Mitochondrial GPAT,
        Microsomal GPAT_hlog1, Microsomal GPAT_hlog2, Microsomal GPAT_hlog3,
        and/or Microsomal GPAT_hlog3_v1 polypeptides to the diagnosis,
        treatment, and/or prevention of various diseases and/or disorders
        related to these polypeptides. The invention further relates to
        screening methods for identifying agonists and antagonists of the
        polynucleotides and polypeptides of the present invention.
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L6 ANSWER 2 OF 12 USPATFULL on STN
2004:25185 Method of treating cerebrotendinous xanthomatosis.
Forman, Barry, Irvine, CA, UNITED STATES
Dussault, Isabelle, Thousand Oaks, CA, UNITED STATES
US 2004019027 A1 20040129
APPLICATION: US 2003-412659 A1 20030411 (10)
PRIORITY: US 2002-371701P 20020412 (60)
DOCUMENT TYPE: Utility; APPLICATION.
AB The present invention provides methods for preventing or treating disorders associated with the degradation of cholesterol and bile alcohols through the use of ligands that interact with pregnane X receptors (PXR). In a preferred embodiment, PXR agonists are used to treat disorders associated with sterol 27-hydroxylase (CYP27) deficiency or mutation. The disorders associated with CYP27 deficiency include but not limited to cerebrotendinous xanthomatosis, cataracts, gallstone, tendon xanthomas, atherosclerosis, hepatomegaly, hypertriglyceridemia, and neurological and neuropsychiatric abnormalities such as peripheral neuropathy and dementia. In another preferred embodiment, PXR agonists are used to prevent or treat disorders that can be alleviated by enhancing the degradation of cholesterol or bile alcohols. The disorders that can be alleviated by enhancing the degradation of cholesterol or bile alcohols include, but not limited to, cardiovascular diseases, hypertension, atherosclerosis, **dyslipidemia**, obesity, hypercholesterolemia, **hyperlipidemia**, hyperlipoproteinemia, hyperchylomicronemia, hyperbetalipoproteinemia, dysbetalipoproteinemia, hyperprebetalipoproteinemia, mixed **hyperlipidemia**, cholestasis, cholesterolosis, gallstone, cataracts, and hepatomegaly.

L6 ANSWER 3 OF 12 USPATFULL on STN
2003:318770 Antisense modulation of sterol regulatory element-binding protein-1 expression.
Freier, Susan M., San Diego, CA, UNITED STATES
Baker, Brenda F., Carlsbad, CA, UNITED STATES
Dobie, Kenneth W., Del Mar, CA, UNITED STATES
Isis Pharmaceuticals Inc. (U.S. corporation)
US 2003224515 A1 20031204
APPLICATION: US 2002-161996 A1 20020604 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Antisense compounds, compositions and methods are provided for modulating the expression of sterol regulatory element-binding protein-1. The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding sterol regulatory element-binding protein-1. Methods of using these compounds for modulation of sterol regulatory element-binding protein-1 expression and for treatment of diseases associated with expression of sterol regulatory element-binding protein-1 are provided.

L6 ANSWER 4 OF 12 USPATFULL on STN
2003:318756 Bone morphogenic protein polynucleotides, polypeptides, and antibodies.
Young, Paul E., Gaithersburg, MD, UNITED STATES
Ruben, Steven M., Brookeville, MD, UNITED STATES
US 2003224501 A1 20031204
APPLICATION: US 2003-366345 A1 20030214 (10)
PRIORITY: US 2002-356749P 20020215 (60)
US 2000-190067P 20000317 (60)
US 2002-348621P 20020117 (60)
US 2002-349356P 20020122 (60)
US 2002-351520P 20020128 (60)
US 2002-354265P 20020206 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel human BMP polypeptides and isolated nucleic acids containing the coding regions of the genes

encoding such polypeptides. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human BMP polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human BMP polypeptides.

L6 ANSWER 5 OF 12 USPATFULL on STN
2003:306402 Bone morphogenic protein polynucleotides, polypeptides, and antibodies.
Young, Paul E., Gaithersburg, MD, UNITED STATES
Ruben, Steven M., Brookeville, MD, UNITED STATES
US 2003215836 A1 20031120
APPLICATION: US 2003-345236 A1 20030116 (10)
PRIORITY: US 2000-190067P 20000317 (60)
US 2002-348621P 20020117 (60)
US 2002-349356P 20020122 (60)
US 2002-351520P 20020128 (60)
US 2002-354265P 20020206 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel human BMP polypeptides and isolated nucleic acids containing the coding regions of the genes encoding such polypeptides. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human BMP polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human BMP polypeptides.

L6 ANSWER 6 OF 12 USPATFULL on STN
2003:153453 Method of preventing **lipodystrophy** syndrome or reversing a pre-existing syndrome in **HIV**-infected patients being treated with antiretroviral agents.
Bihari, Bernard, New York, NY, UNITED STATES
US 2003105121 A1 20030605
APPLICATION: US 2003-341441 A1 20030114 (10)
PRIORITY: US 1999-145843P 19990727 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An improvement in a method of treating an **HIV**/AIDS infection in human patients in which the patient receives antiretroviral therapy and is consequently subjected to significant risk of developing the **lipodystrophy** syndrome in one or more of its characteristics. This risk is reduced, and pre-existing signs of such syndrome from past therapy can be substantially reversed, by the concurrent administration by a therapeutically effective mode of an essentially pure opiate receptor antagonist such as Naltrexone and Naloxone at a low level dosage.

L6 ANSWER 7 OF 12 USPATFULL on STN
2003:146816 Beta-amino heterocyclic dipeptidyl peptidase inhibitors for the treatment or prevention of diabetes.
Edmondson, Scott D., New York, NJ, UNITED STATES
Fisher, Michael H., Ringoes, NJ, UNITED STATES
Kim, Dooseop, Westfield, NJ, UNITED STATES
Maccoss, Malcolm, Freehold, NJ, UNITED STATES
Parmee, Emma R., Scotch Plains, NJ, UNITED STATES
Weber, Ann E., Scotch Plains, NJ, UNITED STATES
Xu, Jinyou, Scotch Plains, NJ, UNITED STATES
US 2003100563 A1 20030529
APPLICATION: US 2002-189603 A1 20020705 (10)
PRIORITY: US 2001-303474P 20010706 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the

dipeptidyl peptidase IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

L6 ANSWER 8 OF 12 USPATFULL on STN
2003:51588 Method of treating the syndrome of **lipodystrophy**.
Clemens, Anton H., Madison, WI, UNITED STATES
CPD, LLC, Madison, WI, UNITED STATES (U.S. corporation)
US 2003036546 A1 20030220
APPLICATION: US 2002-179993 A1 20020625 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treating a human suffering from the Syndrome of **Lipodystrophy** or one or more **HIV**-related abnormalities included therein are provided. One method may include administering, by a pharmaceutically effective mode, a drug composition comprising an opioidergic agent, or alternatively, an opioidergic agent and an insulin secretagogue. The method may also include administering, by a pharmaceutically effective mode, a drug composition comprising an opiate agonist and opiate antagonist, or alternatively, an opiate agonist, opiate antagonist and an insulin secretagogue.

L6 ANSWER 9 OF 12 USPATFULL on STN
2002:69620 Nutritional supplement for patients with type 2 diabetes mellitus for **lipodystrophy**.
Bell, Stacey J., Belmont, MA, United States
Shabert, Judith, Brookline, MA, United States
Functional Foods, Inc., Belmont, MA, United States (U.S. corporation)
US 6365176 B1 20020402
APPLICATION: US 2000-664227 20000918 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Described herein is a nutritional supplement to be incorporated into the diet of a type 2 diabetic or an individual having **lipodystrophy**. The supplement provides active food-grade ingredients to improve the management of blood glucose and blood lipid levels. The supplement additionally aids in the improvement of the effects of platelet aggregation. The supplement should be taken daily during or at the end of the two largest meals, where most of the fat and cholesterol are likely to be ingested.

L6 ANSWER 10 OF 12 USPATFULL on STN
2002:55066 Novel compounds having antitumor activity: process for their preparation and pharmaceutical compositions containing them.
Nanduri, Srinivas, Hyderabad, INDIA
Rajagopal, Sriram, Hyderabad, INDIA
Pothukuchi, Sairam, Hyderabad, INDIA
Pillai, Sunilkumar Bhadramma Kochunarayana, Hyderabad, INDIA
Chakrabarti, Ranjan, Hyderabad, INDIA
DR. REDDY'S RESEARCH FOUNDATION (non-U.S. corporation)
US 2002032229 A1 20020314
APPLICATION: US 2001-775533 A1 20010201 (9)
PRIORITY: IN 2000-892000 20000203
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel derivatives of Andrographolide, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates. The novel derivatives of Andrographolide have the general formula (I) ##STR1##

The andrographolide derivatives represented by general formula (I) are useful for treating cancer, HSV, **HIV**, psoriasis, restonosis, atherosclerosis, other cardiovascular disorders, and can be used as **antiviral**, antimalarial, antibacterial, hepatoprotective, and

immunomodulating agents and for treatment of other metabolic disorders.

L6 ANSWER 11 OF 12 USPATFULL on STN
2002:27515 Novel anticancer compounds : process for their preparation and pharmaceutical compositions containing them.
Nanduri, Srinivas, Hyderabad, INDIA
Pothukuchi, Sairam, Hyderabad, INDIA
Rajagopal, Sriram, Hyderabad, INDIA
Akella, Venkateswarlu, Hyderabad, INDIA
Pillai, Sunilkumar Bhadramma Kochunarayana, Hyderabad, INDIA
Chakrabarti, Ranjan, Hyderabad, INDIA
DR. REDDY'S RESEARCH FOUNDATION (non-U.S. corporation)
US 2002016363 A1 20020207
APPLICATION: US 2001-849586 A1 20010504 (9)
PRIORITY: IN 2000-3542000 20000505
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel anticancer agents, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates. The present invention more particularly relates to novel derivatives of andrographolide, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates. The novel derivatives of andrographolide have the general formula (I). ##STR1##

L6 ANSWER 12 OF 12 USPATFULL on STN
2002:27476 Compounds having anticancer activity : process for their preparation and pharmaceutical compositions containing them.
Nanduri, Srinivas, Andhra Pradesh, INDIA
Rajagopal, Sriram, Andhra Pradesh, INDIA
Akella, Venkateswarlu, Andhra Pradesh, INDIA
DR. REDDY'S RESEARCH FOUNDATION (non-U.S. corporation)
US 2002016324 A1 20020207
APPLICATION: US 2001-849584 A1 20010504 (9)
PRIORITY: IN 2000-3532000 20000505
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel anticancer agents, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates. The present invention more particularly relates to novel derivatives of andrographolide, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates. The novel derivatives of andrographolide have the general formula (I). ##STR1##

=> d l6,cbib,ab,clm,6

L6 ANSWER 6 OF 12 USPATFULL on STN
2003:153453 Method of preventing **lipodystrophy** syndrome or reversing a pre-existing syndrome in **HIV**-infected patients being treated with antiretroviral agents.
Bihari, Bernard, New York, NY, UNITED STATES
US 2003105121 A1 20030605
APPLICATION: US 2003-341441 A1 20030114 (10)
PRIORITY: US 1999-145843P 19990727 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An improvement in a method of treating an **HIV**/AIDS infection in human patients in which the patient receives antiretroviral therapy and is consequently subjected to significant risk of developing the **lipodystrophy** syndrome in one or more of its characteristics. This risk is reduced, and pre-existing signs of such syndrome from past therapy can be substantially reversed, by the concurrent administration

by a therapeutically effective mode of an essentially pure opiate receptor antagonist such as Naltrexone and Naloxone at a low level dosage.

CLM What is claimed is:

1. A method of reducing the risk of the development of the **lipodystrophy** syndrome in a human patient who is already being or is about to be treated for an AIDS/**HIV** infection with substantially a therapeutically effective dosage level of a at least one anti-viral agent subjecting said patient to a significant risk of developing said syndrome, which comprises the step of administering to the patient concurrently with treatment with such anti-viral agent by a pharmacologically effective mode an essentially pure opiate receptor antagonist at a low level dosage which produces substantially the therapeutic results corresponding to those obtained by the administration of Naltrexone at a low dosage level in the range of 1.0 mg. to 10 mg.

2. The method of claim 1 wherein at least one of said anti-viral agents is a protease inhibitor anti-viral agent.

3. The method of claim 1 further comprising the concurrent administration to the patient of a therapeutically effective amount of at least one other anti-viral agent.

4. The method of claim 3 wherein said other anti-viral agent is selected from the non-nucleoside reverse transcription inhibitor.

5. The method of claim 4 wherein a combination of anti-viral agents comprising a protease inhibitor, a non-nucleoside reverse transcription inhibitor. and at least one nucleoside reverse transcription inhibitor are concurrently administered to said patient together with said essentially pure opiate receptor antagonist.

6. The method of claim 1 wherein said antagonist is selected from among Naltrexone and Naloxone.

7. The method of claim 1 wherein said antagonist is Naltrexone.

8. The method of claim 1 wherein said antagonist is administered a low level dosage which produces substantially the therapeutic results corresponding to those obtained by the administration of Naltrexone at a low dosage level in the range of 1.0 mg. to 3 mg.

9. In a method of treatment an **HIV**/AIDS infection in human patients by an anti-viral therapy subjecting said patient to a significant risk of developing over time a **lipodystrophy** syndrome, the improvement comprising the administration to the patient concurrently with said anti-viral therapy by a pharmacologically effective mode of an essentially pure opiate receptor antagonist at a low level dosage which produces substantially the therapeutic results corresponding to those obtained by the administration of Naltrexone at a low dosage level in the range of 1.0 mg. to 10 mg.

10. In a method of treating a patient who has been undergoing treatment of an **HIV**/AIDS infection utilizing an **antiviral** therapy and has developed as a result of such therapy significant characteristics of a **lipodystrophy** syndrome, the improvement comprising the administration to the patient concurrently with said anti-viral therapy by a pharmacologically effective mode of an essentially pure opiate receptor antagonist at a low level dosage which produces substantially the therapeutic results corresponding to those obtained by the administration of Naltrexone at a low dosage level in the range of 1.0 mg. to 10 mg.

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     FILE 'USPATFULL' ENTERED AT 12:57:56 ON 19 FEB 2004
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L1             3 S E4
L2          4172 S (LIPODYSTROPHY OR DYSLIPIDEMIA OR FAT REDISTRIBUTION OR HYPER
L3           894 S L2 AND (RETROVIR? OR HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR H
L4           334 S L3 AND (LIPODYSTROPHY OR DYSLIPIDEMIA)
L5           153 S L4 AND (ANTIVIRAL? OR HAART OR HIGHLY ACTIVE ANTIRETROVIRAL T
L6            12 S L5 AND (LIPODYSTROPHY/CLM OR DYSLIPIDEMIA/CLM OR HYPERLIPIDEM

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COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      56.01      57.27

FILE 'MEDLINE' ENTERED AT 13:09:11 ON 19 FEB 2004

 FILE LAST UPDATED: 18 FEB 2004 (20040218/UP).  FILE COVERS 1958 TO DATE.

 On December 14, 2003, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description
 on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d his

     (FILE 'HOME' ENTERED AT 12:54:31 ON 19 FEB 2004)

     FILE 'USPATFULL' ENTERED AT 12:57:56 ON 19 FEB 2004
               E LENHARD JAMES M/IN
L1             3 S E4
L2          4172 S (LIPODYSTROPHY OR DYSLIPIDEMIA OR FAT REDISTRIBUTION OR HYPER
L3           894 S L2 AND (RETROVIR? OR HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR H
L4           334 S L3 AND (LIPODYSTROPHY OR DYSLIPIDEMIA)
L5           153 S L4 AND (ANTIVIRAL? OR HAART OR HIGHLY ACTIVE ANTIRETROVIRAL T
L6            12 S L5 AND (LIPODYSTROPHY/CLM OR DYSLIPIDEMIA/CLM OR HYPERLIPIDEM

     FILE 'MEDLINE' ENTERED AT 13:09:11 ON 19 FEB 2004

=> e bernard b/au
E1             2     BERNARD ARLETTE/AU
E2             1     BERNARD AUGER M H/AU
E3           113 --> BERNARD B/AU
E4            66     BERNARD B A/AU
E5             3     BERNARD B B/AU
E6             1     BERNARD B D E/AU
E7             2     BERNARD B DE/AU
E8            23     BERNARD B F/AU
E9             1     BERNARD B G/AU
E10            1     BERNARD B H/AU
E11           18     BERNARD B K/AU
E12            5     BERNARD B L/AU

=> s e3
L7           113 "BERNARD B"/AU

=> s l7 and (lipodystrophy or dyslipidemia or hyperlipidemia or fat redistribution)
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          2425 LIPODISTROPHY
          2844 DYSLIPIDEMIA
         20130 HYPERLIPIDEMIA
         90586 FAT
         13654 REDISTRIBUTION
           149 FAT REDISTRIBUTION
                 (FAT(W)REDISTRIBUTION)
L8             0 L7 AND (LIPODYSTROPHY OR DYSLIPIDEMIA OR HYPERLIPIDEMIA OR FAT
                 REDISTRIBUTION)

=> d l7,ti,1-5

L7   ANSWER 1 OF 113     MEDLINE on STN
TI   Apoptosis participates to liver damage in HSV-induced fulminant hepatitis.

L7   ANSWER 2 OF 113     MEDLINE on STN
TI   [Dependence for daily life activities in the prison population in Western
     France].
     Dependance pour les actes de la vie quotidienne en milieu carceral dans la
     region penitentiaire Ouest.

L7   ANSWER 3 OF 113     MEDLINE on STN
TI   [Effect of climatic changes on the phenology of plants and the presence of
     pollen in the air in Switzerland].
     Influence du changement climatique sur la phenologie des plantes et la
     presence de pollens dans l'air en Suisse.

L7   ANSWER 4 OF 113     MEDLINE on STN
TI   Flumazenil vs. placebo in hepatic encephalopathy in patients with
     cirrhosis: a meta-analysis.

L7   ANSWER 5 OF 113     MEDLINE on STN
TI   Comparison of the effect of terlipressin and albumin on arterial blood
     volume in patients with cirrhosis and tense ascites treated by
     paracentesis: a randomised pilot study.


=> d his

     (FILE 'HOME' ENTERED AT 12:54:31 ON 19 FEB 2004)

     FILE 'USPATFULL' ENTERED AT 12:57:56 ON 19 FEB 2004
                E LENHARD JAMES M/IN
L1              3 S E4
L2           4172 S (LIPODYSTROPHY OR DYSLIPIDEMIA OR FAT REDISTRIBUTION OR HYPER
L3            894 S L2 AND (RETROVIR? OR HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR H
L4            334 S L3 AND (LIPODYSTROPHY OR DYSLIPIDEMIA)
L5            153 S L4 AND (ANTIVIRAL? OR HAART OR HIGHLY ACTIVE ANTIRETROVIRAL T
L6             12 S L5 AND (LIPODYSTROPHY/CLM OR DYSLIPIDEMIA/CLM OR HYPERLIPIDEM

     FILE 'MEDLINE' ENTERED AT 13:09:11 ON 19 FEB 2004
                E BERNARD B/AU
L7            113 S E3
L8              0 S L7 AND (LIPODYSTROPHY OR DYSLIPIDEMIA OR HYPERLIPIDEMIA OR FA

=> s l7 and (HIV or human immunodeficiency virus)
        133791 HIV
       8385377 HUMAN
        111808 IMMUNODEFICIENCY
        363680 VIRUS
         42130 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L9              2 L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> d l9,ti,1-2
```

L9 ANSWER 1 OF 2 MEDLINE on STN
TI Successful control of subfulminant hepatitis related to lamivudine-resistant hepatitis B virus in an **HIV**-infected patient.

L9 ANSWER 2 OF 2 MEDLINE on STN
TI Severe acute pancreatitis related to the use of nelfinavir in **HIV** infection: report of a case with positive rechallenge.

=> d his

(FILE 'HOME' ENTERED AT 12:54:31 ON 19 FEB 2004)

FILE 'USPATFULL' ENTERED AT 12:57:56 ON 19 FEB 2004
E LENHARD JAMES M/IN
L1 3 S E4
L2 4172 S (LIPODYSTROPHY OR DYSLIPIDEMIA OR FAT REDISTRIBUTION OR HYPER
L3 894 S L2 AND (RETROVIR? OR HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR H
L4 334 S L3 AND (LIPODYSTROPHY OR DYSLIPIDEMIA)
L5 153 S L4 AND (ANTIVIRAL? OR HAART OR HIGHLY ACTIVE ANTIRETROVIRAL T
L6 12 S L5 AND (LIPODYSTROPHY/CLM OR DYSLIPIDEMIA/CLM OR HYPERLIPIDEM

FILE 'MEDLINE' ENTERED AT 13:09:11 ON 19 FEB 2004
E BERNARD B/AU
L7 113 S E3
L8 0 S L7 AND (LIPODYSTROPHY OR DYSLIPIDEMIA OR HYPERLIPIDEMIA OR FA
L9 2 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s dyslipidemia
L10 2844 DYSLIPIDEMIA

=> s l10 and (HIV or human immunodeficiency virus)
133791 HIV
8385377 HUMAN
111808 IMMUNODEFICIENCY
363680 VIRUS
42130 HUMAN IMMUNODEFICIENCY VIRUS
(HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L11 94 L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l11 and (antiviral? or HAART or highly active antiretroviral therapy)
38568 ANTIVIRAL?
2561 HAART
286887 HIGHLY
381350 ACTIVE
11210 ANTIRETROVIRAL
2102542 THERAPY
2729 HIGHLY ACTIVE ANTIRETROVIRAL THERAPY
(HIGHLY(W)ACTIVE(W)ANTIRETROVIRAL(W)THERAPY)
L12 34 L11 AND (ANTIVIRAL? OR HAART OR HIGHLY ACTIVE ANTIRETROVIRAL THERAPY)

=> d l12,cbib,1-34

L12 ANSWER 1 OF 34 MEDLINE on STN
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=> d l12,cbib,ab,1,11,19,21,22,24,28,30,31,32,34

L12 ANSWER 1 OF 34 MEDLINE on STN
2004045843. PubMed ID: 14746523. **HIV**-Associated Lipodystrophy: Pathogenesis, Prognosis, Treatment, and Controversies. Koutkia Polyxeni; Grinspoon Steven. (Massachusetts General Hospital Program in Nutritional Metabolism and Neuroendocrine Unit, Harvard Medical School, 55 Fruit Street, Boston, Massachusetts 02114; email:. sgrinspoon@partners.org) . Annual review of medicine, (2004) 55 303-17. Journal code: 2985151R. ISSN: 0066-4219. Pub. country: United States. Language: English.
AB Potent antiretroviral agents markedly suppress **HIV** and have dramatically improved the clinical course, prognosis, and survival of **HIV**-infected patients. Unfortunately, **highly active antiretroviral therapy** is often compromised by metabolic complications, including insulin

resistance, **dyslipidemia**, and fat redistribution. Together these changes have been termed the **HIV**-lipodystrophy syndrome, which is estimated to affect a majority of patients treated with potent combination antiretroviral therapy. Routine testing of fasting glucose is recommended for all **HIV**-infected patients, particularly those who are obese, have a family history of diabetes mellitus, or are receiving protease inhibitor therapy. Preliminary investigations have demonstrated the potential utility of insulin-sensitizing agents and lipid-lowering therapies to ameliorate these metabolic disturbances. Patients with **HIV** infection who demonstrate fat redistribution and develop hyperinsulinemia and **dyslipidemia** may be at increased risk of cardiovascular disease. However, the long-term effects on cardiovascular disease have not yet been determined.

L12 ANSWER 11 OF 34 MEDLINE on STN

2003338138 Document Number: 22752454. PubMed ID: 12870543. Evaluation and management of metabolic and coagulative disorders in **HIV**-infected patients receiving **highly active antiretroviral therapy**. Fantoni Massimo; Del Borgo Cosmo; Autore Camillo. (Istituto di Clinica delle Malattie Infettive, Universita Cattolica Sacro Cuore, Roma, Italy.. crif@rom.unicott.it) . AIDS, (2003 Apr) 17 Suppl 1 S162-9. Ref: 85. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB A number of metabolic disorders, including hypercholesterolemia, hypertriglyceridemia, insulin resistance, elevated fasting glucose and diabetes mellitus, were reported in a high proportion of **HIV**-infected patients receiving **highly active antiretroviral therapy** (**HAART**). Less frequently, coagulative disorders were described in patients receiving **HAART**. Since all these metabolic disorders may predispose to coronary heart disease, an early evaluation and treatment is advisable. Existing guidelines for uninfected patients may be applied, taking into account, however, the potential for drug interactions and accumulated toxicity. It may be helpful to stratify all patients in three risk groups to plan regular diagnostic screening. Treatment of **dyslipidemia** and diabetes mellitus should include a first-line approach with non-pharmacological interventions. Statins and fibrates are proposed for **HIV**-infected patients with **HAART**-related hyperlipidemia, but concern has been raised on their potential for interaction with antiretrovirals and hepatic and muscle toxicity. Metformin and thiazolidenediones (or glitazones), hypoglycemic agents that increase insulin sensitivity, are presently under evaluation in diabetic and glucose-intolerant **HIV**-infected patients treated with **HAART**. Glitazones also have a potential for ameliorating the lipodystrophic syndrome. The routine evaluation of coagulative parameters is probably not advisable until a benefit of widespread screening is assessed in prospective studies. A heightened awareness of the possiblity of coagulative disorders, together with controlled trials and basic research, is needed.

L12 ANSWER 19 OF 34 MEDLINE on STN

2003116875 Document Number: 22517127. PubMed ID: 12630645. Lipodystrophy, insulin resistance, diabetes mellitus, **dyslipidemia**, and cardiovascular disease in **human immunodeficiency virus** infection. Tanwani Lal K; Mokshagundam SriPrakash L. (University of Louisville and Veterans Affairs Medical Center, Louisville, KY, USA.. manoharlal626@pol.net) . SOUTHERN MEDICAL JOURNAL, (2003 Feb) 96 (2) 180-8; quiz 189. Ref: 66. Journal code: 0404522. ISSN: 0038-4348. Pub. country: United States. Language: English.

AB The introduction of **highly active antiretroviral therapy** has significantly reduced morbidity and mortality in patients infected with the **human immunodeficiency virus**. Treatment with antiretroviral agents--protease inhibitors in particular--has uncovered a syndrome of abnormal fat redistribution, **dyslipidemia**, and impaired glucose metabolism, collectively termed lipodystrophy syndrome. The cause of the syndrome seems to be multifactorial; however, its exact mechanisms have yet to be elucidated. Accelerated risk for cardiovascular disease is likely to be a major concern in these patients in the future. At this

time, no clinical guidelines are available for the prevention and/or the treatment of lipodystrophy syndrome. The available treatment options range from switching the different antiretroviral drugs and lifestyle modifications to the use of pharmacologic agents to treat patients with **dyslipidemia**, impaired glucose tolerance and/or diabetes, and changes in body composition. This review emphasizes the clinical features, potential molecular mechanisms, and treatment options for patients infected with **human immunodeficiency virus** who have lipodystrophy syndrome.

L12 ANSWER 21 OF 34 MEDLINE on STN

2002632689 Document Number: 22278590. PubMed ID: 12390557. Evaluation and management of **dyslipidemia** in patients with **HIV** infection. Green Michael L. (Yale Primary Care Residency Program, Yale University School of Medicine, Department of Internal Medicine, New Haven, Conn, 06721, USA.. michael.green@yale.edu) . JOURNAL OF GENERAL INTERNAL MEDICINE, (2002 Oct) 17 (10) 797-810. Ref: 129. Journal code: 8605834. ISSN: 0884-8734. Pub. country: United States. Language: English.

AB OBJECTIVE: Persons with **HIV** infection develop metabolic abnormalities related to their antiretroviral therapy and **HIV** infection itself. The objective of this study was to summarize the emerging evidence for the incidence, etiology, health risks, and treatment of dyslipidemias in **HIV** disease. DESIGN: Systematic review of original research with quantitative synthesis. MAIN RESULTS: **Dyslipidemia** is common in persons with **HIV** infection on **highly active antiretroviral therapy** (**HAART**), but methodologic differences between studies preclude precise estimates of prevalence and incidence. The typical pattern includes elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides, which may be markedly elevated. The **dyslipidemia** may be associated with lipodystrophy, insulin resistance, and, rarely, frank diabetes mellitus. Exposure to protease inhibitors (PIs) is associated with this entire range of metabolic abnormalities. PI-naive patients on nucleoside reverse transcriptase inhibitors (NRTIs) may develop lipodystrophy, insulin resistance, hypercholesterolemia, and possibly modest elevations in triglycerides but not severe hypertriglyceridemia, which appears to be linked to PIs alone. Most studies have not found an association between CD4 lymphocyte count or **HIV** viral load and lipid abnormalities. The pathogenesis is incompletely understood and appears to be multifactorial. There are insufficient data to definitively support an increased coronary heart disease risk in patients with **HIV**-related **dyslipidemia**. However, some of the same metabolic abnormalities remain firmly established risk factors in other populations. Patients on **HAART** with severe hypertriglyceridemia may develop pancreatitis or other manifestations of the chylomicronemia syndrome. Some of the metabolic derangements (particularly hypertriglyceridemia) may improve upon replacing a PI with a non-nucleoside reverse transcriptase inhibitor. The limited experience suggests that fibrates, pravastatin, and atorvastatin can safely treat lipid abnormalities in **HIV**-infected patients. CONCLUSIONS: Patients with **HIV** infection on **HAART** should be screened for lipid disorders, given their incidence, potential for morbidity, and possible long-term cardiovascular risk. Treatment decisions are complex and must include assessments of cardiac risk, **HIV** infection status, reversibility of the **dyslipidemia**, and the effectiveness and toxicities of lipid-lowering medications. The multiple potential drug interactions with antiretroviral or other **HIV**-related medications should be considered in lipid-lowering drug selection and monitoring.

L12 ANSWER 22 OF 34 MEDLINE on STN

2002464829 Document Number: 22188988. PubMed ID: 12200758. Increased rates of lipolysis among **human immunodeficiency virus**-infected men receiving **highly active antiretroviral therapy**. Hadigan Colleen; Borgonha Sudhir; Rabe Jessica; Young Vernon; Grinspoon Steven. (Neuroendocrine Unit, Massachusetts General Hospital, Harvard Medical School, Boston 02114, USA.) METABOLISM: CLINICAL AND EXPERIMENTAL, (2002 Sep) 51 (9) 1143-7. Journal code: 0375267. ISSN: 0026-0495. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** (**HIV**) lipodystrophy is associated

with fat redistribution, **dyslipidemia**, and insulin resistance, however, the mechanism of insulin resistance remains unknown. We hypothesized that **HIV**-infected subjects with fat redistribution have increased rates of lipolysis and increased circulating free fatty acid (FFA) levels that contribute to insulin resistance. Anthrompometric and body composition data were obtained and a standard 75-g oral glucose tolerance test (OGTT) was performed on day 1 of the study. Stable isotope infusions of glycerol and palmitate were completed following an overnight fast to assess rates of lipolysis and FFA flux in **HIV**-infected men (n = 19) with and without fat redistribution and healthy controls (n = 8) on day 2. Total FFA levels after standard glucose challenge were increased among **HIV**-infected subjects and positively associated with abdominal visceral adipose tissue area. In contrast, fasting total FFA levels were inversely associated with subcutaneous fat area. Rates of basal lipolysis were significantly increased among **HIV**-infected subjects (rate of appearance [Ra] glycerol, 4.1 +/- 0.2 v 3.3 +/- 0.2 micromol/kg/min in controls; P =.02). Among **HIV**-infected subjects, use of stavudine (P =.006) and the rate of lipolysis (ie, Ra glycerol, P =.02) were strong positive predictors of insulin resistance as measured by insulin response to glucose challenge, controlling for effects of age, body mass index (BMI), waist-to-hip ratio (WHR), and protease inhibitor (PI) exposure. These data demonstrate increased rates of lipolysis and increased total FFA levels in **HIV**-infected subjects and suggest that increased lipolysis may contribute to insulin resistance in this patient population.

L12 ANSWER 24 OF 34 MEDLINE on STN
2002261220 Document Number: 21996227. PubMed ID: 12001033. Selected metabolic and morphologic complications associated with **highly active antiretroviral therapy**. Smith Kimberly Y. (Section of Infectious Diseases, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612, USA.. ksmith2@rush.edu) . JOURNAL OF INFECTIOUS DISEASES, (2002 May 15) 185 Suppl 2 S123-7. Ref: 46. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.
AB Metabolic and morphologic changes have been described in patients with **human immunodeficiency virus** (**HIV**) infection. In the short term, these disorders can be debilitating and may require medical intervention, including alterations in antiretroviral therapy regimens. The long-term consequences have not been fully realized, but are important, particularly in the era of durable **HIV** disease management with **highly active antiretroviral therapy**. This review focuses on 3 of the important morphologic or metabolic changes, namely alterations in body fat distribution, **dyslipidemia**, and lactic acidosis. The prevalence of each of these disorders remains unknown due to varied definitions and difficulty in recognition of the conditions for both the patient and the clinician. Treatment regimens directed at these abnormalities are being developed, but clinical trials are needed to fully ascertain the efficacy and safety of such interventions.

L12 ANSWER 28 OF 34 MEDLINE on STN
2002037209 Document Number: 21597931. PubMed ID: 11762988. Metabolic and morphologic disorders in patients treated with **highly active antiretroviral therapy** since primary **HIV** infection. Narciso P; Tozzi V; D'Offizi G; De Carli G; Orchi N; Galati V; Vincenzi L; Bellagamba R; Carvelli C; Puro V. (Clinical Department, National Institute for Infectious Diseases, Lazzaro Spallanzani-IRCCS, Rome, Italy.. narciso@inmi.it) . ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2001 Nov) 946 214-22. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.
AB Our objective was to describe morphologic and metabolic disorders in patients treated with **highly active antiretroviral therapy** (**HAART**) since primary **HIV** infection (PHI). Our method was prospective evaluation of patients with PHI initiating **HAART** at the time of diagnosis. Outcome measures were: development of hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and of body shape abnormalities indicative of lipodystrophy, assessed through self-reported

questionnaires and physical examination. RESULTS: From May 1997 to April 2001, 41 patients (35 males) with PHI presented at the National Institute for Infectious Diseases "Lazzaro Spallanzani" in Rome, Italy. A protease inhibitor-including regimen was started in 30 patients, and a nonnucleoside reverse transcriptase-inhibitor in 11. Median interval between enrollment and treatment initiation was 30 days (mean 39, range 10-150). Median **HAART** duration was 19 months (mean 21.2, range 3-47). Thirty-eight patients had undetectable (less than 80 cp/mL) **HIV** RNA after a median of 3 months (mean 4.1, range 1-15). Mean CD4 cells count increased from 632/mmc at baseline to 936/mmc at the last follow up. No cases of hyperglycemia (glucose level greater than 110 mg/dL) were observed. After a median of 6 months on **HAART**, 10 patients developed beyond grade 2 (greater than 240 mg/dL) hypercholesterolemia, 5 developed beyond grade 2 (greater than 400 mg/dL) hypertrygliceridemia, and two developed both. Body mass index did not change significantly. Five patients (12.2%) developed lipodystrophy after a median of 14.5 months (mean 15.3, range 2-30), with an incidence of 7.3 per 100 patient-years. CONCLUSIONS: **Dyslipidemia** and lipodystrophy can occur in patients treated with **HAART** since PHI. This risk of should be taken into account when considering this early antiretroviral treatment of **HIV** infection.

L12 ANSWER 30 OF 34 MEDLINE on STN

2001662564 Document Number: 21554913. PubMed ID: 11698228. Improvement of **HAART**-associated insulin resistance and **dyslipidemia** after replacement of protease inhibitors with abacavir. Walli R K; Michl G M; Bogner J R; Goebel F D. (Medizinische Poliklinik, Klinikum der Ludwig-Maximilians-Universitat Munchen, Pettenkoferstr. 8a, D-80336 Munchen, Germany.. rwalli@pk-i.med.uni-muenchen.de) . EUROPEAN JOURNAL OF MEDICAL RESEARCH, (2001 Oct 29) 6 (10) 413-21. Journal code: 9517857. ISSN: 0949-2321. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB OBJECTIVE: To assess the effect of replacing protease inhibitors (PIs) with abacavir on insulin sensitivity and plasma lipids. - Design: Pilot study including 31 patients with sustained virological control on their first PI-containing **HAART** regimen. 16 patients were switched from PIs to abacavir (ABC group), 15 patients continued on PIs (PI group). In all patients, nucleoside-analogue reverse transcriptase inhibitors were continued. METHODS: Insulin sensitivity (using an intravenous insulin tolerance test) and fasting total cholesterol and triglycerides were determined at baseline, month 3, 6, 9 and 12. RESULTS: In the ABC group, there was a significant increase in median insulin sensitivity from baseline within 6 months (+ 49 micromol/l/min), and a significant decrease in both triglycerides (-41mg/dl) and cholesterol (-40mg/dl) at month 3. These changes were sustained through month 12. In addition, a reversal of baseline insulin resistance, hypercholesterolemia and hypertriglyceridemia was observed in the majority of patients. In the PI group, no significant changes in insulin sensitivity, triglycerides and cholesterol were observed. There was a significant correlation between the changes in insulin sensitivity, triglycerides and cholesterol. INTERPRETATION: Switching from PIs to abacavir is associated with an improvement of insulin sensitivity and a decrease of cholesterol and triglycerides in the majority of patients with **HAART**-associated metabolic alterations and therefore might be an alternative for patients to PI-containing **HAART** regimens.

L12 ANSWER 31 OF 34 MEDLINE on STN

2001397226 Document Number: 21341458. PubMed ID: 11448728. Metabolic complications associated with antiretroviral therapy. Jain R G; Furfine E S; Pedneault L; White A J; Lenhard J M. (Department of Metabolic Diseases, GlaxoSmithKline Inc., 5 Moore Drive, 27709, Research Triangle Park, NC, USA.) ANTIVIRAL RESEARCH, (2001 Sep) 51 (3) 151-77. Ref: 150. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB Mortality rates in the **HIV**-infected patient population have decreased with the advent of **highly active antiretroviral therapy** (**HAART**) for the treatment of AIDS. Due to the chronic nature of **HAART**, long-term metabolic complications are associated with therapy, such as

hyperlipidemia, fat redistribution and diabetes mellitus. Currently, all of these symptoms are classified as the lipodystrophy (LD) syndrome(s). However, hyperlipidemia and fat redistribution occur independently, indicating there may be multiple syndromes associated with **HAART**. Although fat gain/loss and **dyslipidemia** occur in protease inhibitor (PI) naive patients treated with nucleoside reverse transcriptase inhibitors (NRTIs), combination therapies (PI and NRTI) accelerate the syndrome. Recent clinical trials, cell culture and animal studies indicate that these effects are not drug class specific and select PIs, NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) can be associated with metabolic complications. Moreover, the effects can vary between various members of the same class of antiretroviral agents (i.e. not all PIs cause the same adverse reactions) and may be influenced by duration of infection, genetics and environmental factors. Although **HAART** increases the risk of metabolic complications, this does not outweigh the benefits of survival. In this review, we summarize the latest clinical and scientific information on these metabolic complications, examine current hypotheses explaining the syndromes and comment on the existing methods available to manage these metabolic side effects.

L12 ANSWER 32 OF 34 MEDLINE on STN

2000269794 Document Number: 20269794. PubMed ID: 10807787. Alteration of tumor necrosis factor-alpha T-cell homeostasis following potent antiretroviral therapy: contribution to the development of **human immunodeficiency virus**-associated lipodystrophy syndrome. Ledru E; Christeff N; Patey O; de Truchis P; Melchior J C; Gougeon M L. (Unite d'Oncologie Virale, URA CNRS 1930, Departement SIDA et Retrovirus, Institut Pasteur, Paris, France.) BLOOD, (2000 May 15) 95 (10) 3191-8. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB **Highly-active antiretroviral therapy** (**HAART**) has lead to a dramatic decrease in the morbidity of patients infected with the **human immunodeficiency virus** (**HIV**). However, metabolic side effects, including lipodystrophy-associated (LD-associated) **dyslipidemia**, have been reported in patients treated with antiretroviral therapy. This study was designed to determine whether successful **HAART** was responsible for a dysregulation in the homeostasis of tumor necrosis factor-alpha (TNF-alpha), a cytokine involved in lipid metabolism. Cytokine production was assessed at the single cell level by flow cytometry after a short-term stimulation of peripheral blood T cells from **HIV**-infected (**HIV**(+)) patients who were followed during 18 months of **HAART**. A dramatic polarization to TNF-alpha synthesis of both CD4 and CD8 T cells was observed in all patients. Because it was previously shown that TNF-alpha synthesis by T cells was highly controlled by apoptosis, concomitant synthesis of TNF-alpha and priming for apoptosis were also analyzed. The accumulation of T cells primed for TNF-alpha synthesis is related to their escape from activation-induced apoptosis, partly due to the cosynthesis of interleukin-2 (IL-2) and TNF-alpha. Interestingly, we observed that LD is associated with a more dramatic TNF-alpha dysregulation, and positive correlations were found between the absolute number of TNF-alpha CD8 T-cell precursors and lipid parameters usually altered in LD including cholesterol, triglycerides, and the atherogenic ratio apolipoprotein B (apoB)/apoA1. Observations from the study indicate that **HAART** dysregulates homeostasis of TNF-alpha synthesis and suggest that this proinflammatory response induced by efficient antiretroviral therapy is a risk factor of LD development in **HIV**(+) patients.

L12 ANSWER 34 OF 34 MEDLINE on STN

2000086967 Document Number: 20086967. PubMed ID: 10620100. Influence of protease inhibitor therapy on lipoprotein metabolism. Berthold H K; Parhofer K G; Ritter M M; Addo M; Wasmuth J C; Schliefer K; Spengler U; Rockstroh J K. (Department of Internal Medicine I, University of Bonn, Germany.. berthold@uni-bonn.de) . JOURNAL OF INTERNAL MEDICINE, (1999 Dec) 246 (6) 567-75. Journal code: 8904841. ISSN: 0954-6820. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVES: Protease inhibitors are efficient drugs as part of **highly**

active antiretroviral therapy. They have been shown to cause hyper
and dyslipoproteinemia. Since antiretroviral therapy is able to delay disease progression and possibly extend life expectancy in **HIV**-infected individuals, the precise nature of serum lipid disturbances may become of clinical interest with respect to its atherogenicity and to finding treatment options. DESIGN: We investigated prospectively, in 19 subsequent **HIV**-positive male patients (mean age 42 +/- 13 years), multiple lipid parameters in plasma, before and during treatment with a protease inhibitor (nelfinavir, ritonavir, or indinavir) and two nucleoside analogue reverse transcriptase inhibitors (NRTI). The median (range) treatment duration was 22 (7-40) weeks. 12 patients were treatment-naive; 7 had already NRTI medication at baseline. RESULTS: Total cholesterol increased by 28 mg dL-1 (95% CI: + 7 to + 48, baseline 158 +/- 53, P = 0.01), triglycerides increased by 96 mg dL-1 (+ 22 to + 170, baseline 152 +/- 91, P = 0.014), HDL cholesterol was unchanged, LDL cholesterol was slightly but not significantly elevated, VLDL cholesterol increased by 20 mg dL-1 (+ 9 to + 31, baseline 33 +/- 21, P = 0.001), VLDL triglycerides increased by 86 mg dL-1 (+ 22 to + 150, baseline 128 +/- 91, P = 0. 01). The ratio of total cholesterol to HDL cholesterol increased by 1.2 (+ 0.7 to + 1.7, baseline 4.8 +/- 1.5, P = 0.0001) and the ratio of HDL2 to HDL3 decreased by 0.06 (-0.02 to -0.09, baseline 0.47 +/- 0.11, P = 0.005). (Conversion factors, mg dL-1 to mmol L-1: 0.0259 for cholesterol, 0.0114 for triglycerides.) CONCLUSIONS: The data indicate that the predominant feature of **dyslipidemia** under protease inhibitors is an increase in triglyceride-containing lipoproteins. This observation is in accordance with the hypothesis of increased apoptosis of peripheral adipocytes, release of free fatty acids and subsequent increased synthesis of VLDL. The lipid profile, based on the ratio of total cholesterol to HDL cholesterol and the ratio HDL2 to HDL3, is significantly more atherogenic.

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L1   ANSWER 1 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New fluoropyrrolidines useful as dipeptidyl peptidase inhibitors for
     treating e.g. metabolic disorders, gastrointestinal disorders, viral
     disorders, inflammatory disorders, diabetes and obesity.

L1   ANSWER 2 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New fluoropyrrolidine derivatives are dipeptidyl peptidase inhibitors used
     for treating e.g. viral, inflammatory and autoimmune disorders, diabetes
     and obesity.

L1   ANSWER 3 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New pyrrolidine derivatives are dipeptidyl peptidase inhibitors used for
     treating e.g. HIV infection, inflammatory and autoimmune disorders, tumors
     and diabetes.

L1   ANSWER 4 OF 8  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Pharmaceutical composition for the treatment of diabetes mellitus,
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particularly non insulin dependent diabetes mellitus comprises a dipeptidyl peptidase inhibitor and another antidiabetic agent.

L1 ANSWER 5 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Non-invasive, rapid diagnostic and drug screening methods, e.g. for diagnosis of lipodystrophy, involving measurement of temperature differences using infrared thermography.

L1 ANSWER 6 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Methods for detecting retroviral therapeutic agents, such as protease inhibitors, for their capacity to affect lipodystrophy or dyslipidemia.

L1 ANSWER 7 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI New thiazolidinone compounds are peroxisome proliferator activated receptor gamma antagonists for treating e.g. diabetes and cancer.

L1 ANSWER 8 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Screening of test agent such as drugs for its ability to produce thermodynamic change in cell-free sample using infrared thermography.

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AN 2000-482837 [42] WPIDS
DNN N2000-358934 DNC C2000-145331
TI Methods for detecting retroviral therapeutic agents, such as protease inhibitors, for their capacity to affect lipodystrophy or dyslipidemia.
DC B04 D16 P14 S03
IN **LENHARD, J M**
PA (GLAX) GLAXO GROUP LTD
CYC 91
PI WO 2000042211 A1 20000720 (200042)* EN 77p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000027301 A 20000801 (200054)
EP 1144673 A1 20011017 (200169) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2002534131 W 20021015 (200282) 84p
MX 2001007290 A1 20020101 (200362)
ADT WO 2000042211 A1 WO 2000-US1205 20000119; AU 2000027301 A AU 2000-27301 20000119; EP 1144673 A1 EP 2000-905651 20000119, WO 2000-US1205 20000119; JP 2002534131 W JP 2000-593768 20000119, WO 2000-US1205 20000119; MX 2001007290 A1 WO 2000-US1205 20000119, MX 2001-7290 20010718
FDT AU 2000027301 A Based on WO 2000042211; EP 1144673 A1 Based on WO 2000042211; JP 2002534131 W Based on WO 2000042211; MX 2001007290 A1 Based on WO 2000042211
PRAI US 1999-146309P 19990727; US 1999-116300P 19990119; US 1999-137620P 19990604
AB WO 200042211 A UPAB: 20000905
NOVELTY - Methods for detecting retroviral therapeutic agents (RTA), such as protease inhibitors, for their capacity to affect lipodystrophy or dyslipidemia, are new.

DETAILED DESCRIPTION - Methods for detecting retroviral therapeutic agents (RTA), such as protease inhibitors, for their capacity to affect lipodystrophy or dyslipidemia, are new.

INDEPENDENT CLAIMS are provided for the following:

(1) a method (M1) of screening an RTA for its capacity to affect lipodystrophy or dyslipidemia in a patient, comprising:

(a) administering the RTA to a mesenchymal stem cell or pre-adipocyte

cell under culture conditions appropriate for adipogenesis; and

(b) monitoring the cell for an inhibition of adipogenesis, where inhibition of adipogenesis indicates the RTA has the capacity to increase lipodystrophy or dyslipidemia in the patient;

(2) a method (M2) of screening an RTA for its capacity to affect lipodystrophy or dyslipidemia in a patient, comprising:

(a) administering the RTA to a cell capable of metabolizing lipids under conditions permissible for lipogenesis or lipolysis; and

(b) monitoring net lipogenesis or lipolysis in the cell, where a change in net lipogenesis or lipolysis in the cell indicates the protease inhibitor can affect lipodystrophy or dyslipidemia;

(3) a method (M3) of screening an RTA for its capacity to affect lipodystrophy or dyslipidemia in a patient, comprising:

(a) administering the RTA to a cell capable of metabolizing lipids under conditions permissible for metabolizing lipids; and

(b) monitoring the expression of a peroxisome proliferator activated receptor gamma (PPAR gamma):retinoid X receptor (RXR)-regulated gene in the cell, where a change in gene expression of the PPAR gamma :RXR-regulated gene indicates the RTA can affect lipodystrophy or dyslipidemia;

(4) a method (M4) of screening a protease inhibitor (PI) for its capacity to affect lipodystrophy, dyslipidemia, or retinoid-associated toxicity in a patient, comprising:

(a) administering the PI to a cell containing a retinoid-regulated gene in the presence of a retinoid; and

(b) monitoring the cell for a change in the expression of the retinoid-activated gene, where a change in the expression of the retinoid-activated gene indicates the PI can affect lipodystrophy, dyslipidemia, or retinoid-associated toxicity;

(5) a method (M5) of screening a compound for its potential to effect fat metabolism comprising:

(a) contacting a PPAR gamma receptor-ligand complex with the compound; and

(b) monitoring the complex for displacement of the receptor ligand from the complex or for binding of the compound to the complex, where a compound that displaces the receptor or a compound that binds to the complex receptor has a potential to effect fat metabolism;

(6) a method (M6) of screening an RTA for its capacity to affect lipodystrophy or dyslipidemia in a patient, comprising:

(a) administering the RTA to a mammal susceptible to diet-induced obesity; and

(b) monitoring the mammal for an increase in serum lipids, blood urea nitrogen or glucose, where the increase in net serum lipids, blood urea nitrogen or glucose indicates that RTA has the capacity to increase lipodystrophy or dyslipidemia in a patient;

(7) a method (M7) of screening an RTA for its capacity to affect lipodystrophy or dyslipidemia in a patient, comprising:

(a) administering the RTA to a mammal susceptible to diet-induced obesity; and

(b) monitoring net fat deposition in the mammal, where a change in net fat deposition indicates the RTA can affect lipodystrophy or dyslipidemia;

(8) a method (M8) of screening an RTA for its capacity to affect lipodystrophy, dyslipidemia or retinoid associated toxicities in a patient, comprising:

(a) administering the RTA to a cell containing a retinoid-regulated gene in the presence of a retinoid; and

(b) monitoring the mammal for a change in the expression of a retinoid-activated gene, where a change in the expression of the retinoid-activated gene indicates the RTA can affect lipodystrophy, dyslipidemia, or retinoid associated toxicities;

(9) a transgenic mouse whose somatic cells comprise and express a transgene conferring sensitivity to an RTA, where the total native and transgene expressed in the transgenic mouse is higher than the native gene expressed in a non-transgenic mouse and the transgenic mouse has a phenotype of increased sensitivity to the RTA;

(10) a transgenic mouse whose somatic cells comprise and overexpress ubiquitously in all tissues a transgene conferring sensitivity to an RTA, where the total native and transgene expressed in the transgenic mouse is higher than the native gene expressed in a non-transgenic mouse and the transgenic mouse has a phenotype of increased sensitivity to the RTA;

(11) a method (M9) of identifying a compound for treating RTA-induced lipodystrophy or dyslipidemia in a mammal, comprising:

(a) administering the compound to an RTA-sensitive mouse; and

(b) monitoring the mouse for a change in the expression of a gene and/or the activity of a gene product associated with lipodystrophy or dyslipidemia, a change in fat distribution, and/or a change in serum lipids, where the change is a change in the expression of the gene and/or the activity of the gene product, an increase in fat distribution, or a decrease in serum lipids which indicates the compound has the capacity to decrease lipodystrophy or dyslipidemia in the mammal;

(12) a method (M10) of detecting a capacity of a compound to cause RTA-induced lipodystrophy or dyslipidemia in a mammal, comprising:

(a) administering the compound to an RTA-sensitive mouse; and

(b) monitoring the mouse for a change in expression of a gene and/or the activity of a gene product associated with lipodystrophy, dyslipidemia or retinoid associated toxicities in the mouse, a change in fat distribution, and/or a change in serum lipids, where the change is a change in the expression of the gene and/or the activity of the gene product, an increase in fat distribution, and/or a decrease in serum lipids; and

(13) a method (M11) of classifying a patient as being susceptible to RTA-induced lipodystrophy or dyslipidemia, comprising:

(a) administering RTA to the patient; and

(b) monitoring the patient for a change in the expression of a gene and/or the activity of a gene associated with lipodystrophy, dyslipidemia or retinoid associated toxicities, a change in fat distribution, and/or a change in serum lipids, where a change in the expression of the gene and/or the activity of the gene product, an increase in fat distribution, and/or a decrease in serum lipids indicates the patient may be susceptible to lipodystrophy or dyslipidemia.

USE - The method is useful for screening a protease inhibitor for its capacity to affect symptoms or clinical conditions associated with lipodystrophy or dyslipidemia and related metabolic disorders such as metabolic syndrome X, obesity, cardiovascular disorders and impaired glucose tolerance in diabetes.

Dwg.0/9

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=> d his

     (FILE 'HOME' ENTERED AT 18:32:09 ON 19 FEB 2004)

     FILE 'WPIDS' ENTERED AT 18:43:10 ON 19 FEB 2004
               E LENHARD J M/IN
L1             8 S E3

=> s (lipodystrophy or dyslipidemia or hyperlipidemia or fat redistribution or adipogenesis)
            64 LIPODYSTROPHY
           545 DYSLIPIDEMIA
          1564 HYPERLIPIDEMIA
         36581 FAT
          2401 REDISTRIBUTION
             1 FAT REDISTRIBUTION
               (FAT(W)REDISTRIBUTION)
            52 ADIPOGENESIS
L2          2037 (LIPODYSTROPHY OR DYSLIPIDEMIA OR HYPERLIPIDEMIA OR FAT REDISTRI
               BUTION OR ADIPOGENESIS)

=> s l2 and (HIV or human immunodeficiency virus)
          17025 HIV
         139635 HUMAN
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          6818 IMMUNODEFICIENCY
         34259 VIRUS
          4414 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L3          175 L2 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l3 and (HAART or highly active antiretroviral therapy)
            33 HAART
        147980 HIGHLY
        366770 ACTIVE
           189 ANTIRETROVIRAL
         47532 THERAPY
            26 HIGHLY ACTIVE ANTIRETROVIRAL THERAPY
                 (HIGHLY(W)ACTIVE(W)ANTIRETROVIRAL(W)THERAPY)
L4            3 L3 AND (HAART OR HIGHLY ACTIVE ANTIRETROVIRAL THERAPY)

=> d l4,ti,1-3

L4   ANSWER 1 OF 3  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Use of leptin, its analog or derivative for treatment of metabolic
     abnormalities associated with lipoatrophy or acquired form of lipoatrophy
     disease in human patient.

L4   ANSWER 2 OF 3  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Reducing side-effects of nucleoside biosynthesis inhibitors, e.g.
     anti-AIDS drugs, using agents increasing concentration of pyrimidine base
     components for nucleic acid biosynthesis in the body.

L4   ANSWER 3 OF 3  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Treatment of dysmorphic/dysmetabolic syndrome in acquired immunodeficiency
     syndrome patients, using human growth hormone or analog, useful for
     treating symptoms such as buffalo hump or crix belly.


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=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    44.97      48.75

FILE 'USPATFULL' ENTERED AT 18:50:28 ON 19 FEB 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 19 Feb 2004 (20040219/PD)
FILE LAST UPDATED: 19 Feb 2004 (20040219/ED)
HIGHEST GRANTED PATENT NUMBER: US6694518
HIGHEST APPLICATION PUBLICATION NUMBER: US2004034897
CA INDEXING IS CURRENT THROUGH 19 Feb 2004 (20040219/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 19 Feb 2004 (20040219/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2003

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>>>  original, i.e., the earliest published granted patents or         <<<
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>>>  publications, starting in 2001, for the inventions covered in     <<<
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>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
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>>>  classifications, or claims, that may potentially change from        <<<
>>>  the earliest to the latest publication.                              <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s (stem cell?/clm)
         37572 STEM/CLM
        230453 CELL?/CLM
L5        2263 (STEM CELL?/CLM)
                 ((STEM(W)CELL?)/CLM)

=> s l5 and (mesenchymal stem cell?/clm)
           418 MESENCHYMAL/CLM
         37572 STEM/CLM
        230453 CELL?/CLM
           191 MESENCHYMAL STEM CELL?/CLM
                 ((MESENCHYMAL(W)STEM(W)CELL?)/CLM)
L6         191 L5 AND (MESENCHYMAL STEM CELL?/CLM)

=> d l6,cbib,ab,185-191

L6   ANSWER 185 OF 191  USPATFULL on STN
95:71140 Shaped, swollen demineralized bone and its use in bone repair.
    Prewett, Annamarie B., Little Silver, NJ, United States
    Stikeleather, Roger C., Doylestown, PA, United States
    Bogdansky, Simon, Marlboro, NJ, United States
    O'Leary, Robert K., Spring Lake, NJ, United States
    Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
    US 5439684 19950808
    APPLICATION: US 1994-184306  19940121 (8)
    DOCUMENT TYPE: Utility; Granted.
AB     A shaped piece of swollen demineralized bone which can also be
       plasticized is provided for use in surgical bone repair.

L6   ANSWER 186 OF 191  USPATFULL on STN
94:44221 Demineralized bone particles and flowable osteogenic composition
    containing same.
    Prewett, Annamarie B., Little Silver, NJ, United States
    Stikeleather, Roger C., Doylestown, PA, United States
    Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
    US 5314476 19940524
    APPLICATION: US 1993-119882  19930910 (8)
    DOCUMENT TYPE: Utility; Granted.
AB     Demineralized bone particles having a median length to median thickness
       ratio of at least about 10:1 are incorporated in an osteogenic
       composition useful for repairing bone defects.

L6   ANSWER 187 OF 191  USPATFULL on STN
94:26287 Shaped, swollen demineralized bone and its use in bone repair.
    Prewett, Annamarie B., Little Silver, NJ, United States
    Stikeleather, Roger C., Doylestown, PA, United States
    Bogdansky, Simon, Marlboro, NJ, United States
    O'Leary, Robert K., Spring Lake, NJ, United States
    Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
    US 5298254 19940329
    APPLICATION: US 1991-809580  19911217 (7)
    DOCUMENT TYPE: Utility; Granted.
AB     A shaped piece of swollen demineralized bone which can also be
       plasticized is provided for use in surgical bone repair.

L6   ANSWER 188 OF 191  USPATFULL on STN
94:17799 Flowable demineralized bone powder composition and its use in bone
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repair.
O'Leary, Robert K., Spring Lake, NJ, United States
McBrayer, Patrick A., Yardley, PA, United States
Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
US 5290558 19940301
APPLICATION: US 1990-573458 19900827 (7)
DOCUMENT TYPE: Utility; Granted.
AB A flowable demineralized bone powder composition is provided for use in surgical bone repair.

L6 ANSWER 189 OF 191 USPATFULL on STN
94:11227 Swollen demineralized bone particles, flowable osteogenic composition containing same and use of the composition in the repair of osseous defects
.
Bogdansky, Simon, Marlboro, NJ, United States
O'Leary, Robert K., Spring Lake, NJ, United States
Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
US 5284655 19940208
APPLICATION: US 1992-830942 19920204 (7)
DOCUMENT TYPE: Utility; Granted.
AB Swollen demineralized bone particles are formulated into a flowable osteogenic composition which is useful in the repair of osseous defects.

L6 ANSWER 190 OF 191 USPATFULL on STN
93:56458 Method for treating connective tissue disorders.
Caplan, Arnold I., 1300 Oakridge Dr., Cleveland Heights, OH, United States 44121
Haynesworth, Stephen E., 3643 Antisdale Rd., Cleveland Heights, OH, United States 44118
US 5226914 19930713
APPLICATION: US 1990-614912 19901116 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to various processes and devices for utilizing isolated and culturally expanded marrow-derived mesenchymal cells (i.e. mesenchymal stem cells) for treating skeletal and other connective tissue disorders.

L6 ANSWER 191 OF 191 USPATFULL on STN
93:24463 Method for enhancing the implantation and differentiation of marrow-derived mesenchymal cells.
Caplan, Arnold I., 1300 Oakridge Dr., Cleveland Heights, OH, United States 44121
Haynesworth, Stephen E., 3643 Antisdale Rd., Cleveland Heights, OH, United States 44118
US 5197985 19930330
APPLICATION: US 1990-614915 19901116 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to a method and device for enhancing the implantation and differentiation of marrow-derived mesenchymal cells (i.e. mesenchymal stem cells). The method and device of the invention are an effective means for treating skeletal and other connective tissue disorders.

=> d l6,cbib,ab,clm,185-191

L6 ANSWER 185 OF 191 USPATFULL on STN
95:71140 Shaped, swollen demineralized bone and its use in bone repair.
Prewett, Annamarie B., Little Silver, NJ, United States
Stikeleather, Roger C., Doylestown, PA, United States
Bogdansky, Simon, Marlboro, NJ, United States
O'Leary, Robert K., Spring Lake, NJ, United States
Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
US 5439684 19950808

APPLICATION: US 1994 104500 19940121 (8)
DOCUMENT TYPE: Utility; Granted.

AB A shaped piece of swollen demineralized bone which can also be plasticized is provided for use in surgical bone repair.

CLM What is claimed is:

1. A kit for swelling, disinfecting and/or plasticizing demineralized bone, said kit comprising (a) a first sealed vessel comprising the bone immersed in a swelling medium, (b) a second sealed vessel comprising disinfecting and/or plasticizing medium, and (c) means for accessing the interior of said first vessel for (1) draining off said swelling medium and (2) placing said first sealed vessel in open communication with said second sealed vessel containing said disinfecting and/or plasticizing medium, wherein said swelling medium is selected from a member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound ester, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound ester and mixtures thereof, and the polyhydroxy compound is selected from the group consisting of acyclic polyhydric alcohols, non-reducing sugars, sugar alcohols, sugar acids, monosaccharides, disaccharides, water-soluble or water dispersible oligosaccharides, polysaccharides, polyalkylene glycols and mixtures thereof.

2. The kit of claim 1 wherein the bone is shaped.

3. The kit of claim 1 wherein the swelling medium is selected from the group consisting of glycerol, glycerol monoester and glycerol diester.

4. The kit of claim 1 wherein the swelling medium is selected from the group consisting of monosaccharide, monosaccharide ester, disaccharide, disaccharide ester, oligosaccharide, oligosaccharide ester and mixtures thereof.

5. The kit of claim 1 wherein the swelling medium is selected from the group consisting of fructose, glucose and mixtures thereof.

6. The kit of claim 1 wherein the swelling medium is a liquid solution of sucrose.

7. The kit of claim 1 wherein the swelling medium is an aqueous solution of sucrose.

8. The kit of claim 1 wherein the swelling medium is a liquid solution of a fatty acid monoester of glycerol.

9. The kit of claim 1 wherein the swelling medium is a fatty acid monoester dissolved in a solvent which is a different liquid polyhydroxy compound and/or ester thereof.

10. The kit of claim 1 wherein the swelling medium is a fatty acid monoester dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

11. The kit of claim 1 wherein the swelling medium is glycerol monolaurate dissolved in a solvent.

12. The kit of claim 1 wherein the swelling medium is glycerol monolaurate dissolved in a solvent which is a different liquid polyhydroxy compound and/or ester thereof.

13. The kit of claim 1 wherein the swelling medium is glyceryl monolaurate dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

14. The kit of claim 1 wherein the demineralized bone is derived from

cortical bone, cancellous and/or corticocancellous autogenous, xenogeneic and/or allogeneic bone tissue.

15. The kit of claim 1 wherein the demineralized bone is derived from cortical allogeneic bone tissue.

16. The kit of claim 1 wherein a composition comprising the bone in said first vessel (a) contains from about 5 to about 90 weight percent demineralized bone and from about 10 to about 95 weight percent swelling medium.

17. The kit of claim 16 wherein said composition contains from about 20 to about 80 weight percent demineralized bone and from about 20 to about 80 weight percent swelling medium.

18. The kit of claim 1 wherein the bone contains at least one additional ingredient selected from the group consisting of antiviral agent, antimicrobial agent, antibiotic agent, amino acid, magainin, peptide, vitamin, protein synthesis co-factor, hormone, endocrine tissue, synthesizer, enzyme, polymer-cell scaffolding agent with parenchymal cells, surface cell antigen eliminator, angiogenic drug, polymeric drug carrier, collagen lattice, antigenic agent, cytoskeletal agent, **mesenchymal stem cells**, bone digester, antitumor agent, cellular attractant, fibronectin, growth hormone cellular attachment agent, immunosuppressant, nucleic acid, surface active agent, hydroxyapatite and penetration enhancer.

19. The kit of claim 2 wherein the bone is shaped in the form of a sheet, ring, disk, cube, cylinder or tube.

20. The kit of claim 1 wherein the bone is shaped to have substantially regular geometry and/or at least one dimension greater than about 12 mm.

21. The kit of claim 1 wherein the polyhydroxy compound possesses from 2 to about 18 carbon atoms.

22. A kit for swelling, disinfecting and/or plasticizing demineralized bone, said kit comprising (a) a first sealed vessel comprising the bone immersed in a swelling medium, (b) a second sealed vessel comprising disinfecting and/or plasticizing medium, and (c) means for accessing the interior of said first vessel for (1) draining off said swelling medium and (2) placing said first sealed vessel in open communication with said second sealed vessel containing said disinfecting and/or plasticizing medium, wherein the swelling medium is selected from the group consisting of ethylene glycol, diethylene glycol, triethylene glycol, 1,2-propanediol, trimethylolethane, trimethylopropane, erythritol, pentaerythritol, polyethylene glycols, xylitol, sorbitol, mannitol, dulcitol, arabinose, xylose, ribose, adonitol, arabitol, rhamose, inositol, fructose, galactose, glucose, mannose, sorbose, sucrose, maltose, lactose, maltitol, lactitol, stachyose, maltopentaose, cyclomaltohexaose, carrageenan, agar, alginic acid, guar gum, gum tragacanth, locust bean gum, gum arabic, xanthan gum, amylose and mixtures thereof.

23. The kit of claim 19 wherein the bone is shaped in the form of a tubular screw stabilizer or sleeve, a substantially cylindrical bone plug, a pledget, a solid or hollow wedge, a ribbon or tape, a rope, a sheet or patch, a liner or a clip.

24. The kit of claim 1 wherein said disinfecting and/or plasticizing solution comprises an aqueous solution.

25. The kit of claim 24 wherein said aqueous solution includes, in an amount suitable to disinfect said demineralized bone, a disinfectant selected from the group consisting of gentamicin sulfate, bacitracin, polymyxin B, neomycin and sodium cefazolin and mixtures thereof.

26. The kit of claim 25 wherein the swelling medium is glycerol.

L6 ANSWER 186 OF 191 USPATFULL on STN
94:44221 Demineralized bone particles and flowable osteogenic composition containing same.
Prewett, Annamarie B., Little Silver, NJ, United States
Stikeleather, Roger C., Doylestown, PA, United States
Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
US 5314476 19940524
APPLICATION: US 1993-119882 19930910 (8)
DOCUMENT TYPE: Utility; Granted.

AB Demineralized bone particles having a median length to median thickness ratio of at least about 10:1 are incorporated in an osteogenic composition useful for repairing bone defects.

CLM What is claimed is:

1. A flowable osteogenic composition comprising a quantity of entangled demineralized bone particles of which at least about 60 weight percent of said particles is made up of demineralized bone particles substantially in the shape of threads or filaments having a median length to median thickness ratio of at least about 10:1 and up to about 500:1, a median length of from about 2 mm to about 400 mm and a median thickness of from about 0.05 mm to about 2 mm and a sufficient amount of biocompatible fluid carrier to provide a flowable mass, whereby said osteogenic composition maintains its cohesiveness and resists erosion subsequent to being applied to an osseus defect site.

2. The osteogenic composition of claim 1 of which at least about 60 weight percent of said particles is made up of demineralized bone particles possessing a median length of from about 10 mm to about 100 mm, a median thickness of from about 0.08 mm to about 1.5 mm and a median length to median thickness ratio of from about 50:1 to about 100:1.

3. The osteogenic composition of claim 1 in which the demineralized bone particles are obtained from cortical autogenic, cortical allogeneic, cortical xenogeneic, cancellous autogenic, cancellous allogeneic, cancellous xenogeneic, corticocancellous autogenic, corticocancellous allogeneic or corticocancellous xenogeneic bone.

4. The osteogenic composition of claim 1 in which the demineralized bone particles are obtained from porcine bone.

5. The osteogenic composition of claim 1 containing from about 5 to about 90 weight percent demineralized bone particles and from about 10 to about 95 weight percent carrier.

6. The osteogenic composition of claim 1 containing from about 20 to about 80 weight percent demineralized bone particles and from about 20 to about 80 weight percent carrier.

7. The osteogenic composition of claim 1 wherein the carrier is a member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound derivative, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound derivative and mixtures thereof.

8. The osteogenic composition of claim 7 wherein the carrier is selected from the group consisting of glycerol glycerol monoester and glycerol diester.

9. The osteogenic composition of claim 7 wherein the carrier is selected from the group consisting of monosaccharide, monosaccharide derivative, disaccharide, disaccharide derivative, oligosaccharide, oligosaccharide derivative and mixtures thereof.

10. The osteogenic composition of claim 7 wherein the carrier is selected from the group consisting of fructose, glucose and mixtures thereof.

11. The osteogenic composition of claim 7 wherein the carrier is a liquid solution of sucrose.

12. The osteogenic composition of claim 7 wherein the carrier is an aqueous solution of sucrose.

13. The osteogenic composition of claim 7 wherein the carrier is a liquid solution of a fatty acid monoester of glycerol.

14. The osteogenic composition of claim 7 wherein the carrier is a fatty acid monoester dissolved in a solvent which is selected from at least one of a different liquid polyhydroxy compound and derivative of said different liquid polyhydroxy compound.

15. The osteogenic composition of claim 7 wherein the carrier is a fatty acid monoester dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

16. The osteogenic composition of claim 7 wherein the carrier is glycerol monolaurate dissolved in a solvent.

17. The osteogenic composition of claim 7 wherein the carrier is glycerol monolaurate dissolved in a solvent which is a different liquid polyhydroxy compound and/or derivative thereof.

18. The osteogenic composition of claim 7 wherein the carrier is glycerol monolaurate dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

19. The osteogenic composition of claim 1 containing at least one additional ingredient selected from the group consisting of antiviral agent, antimicrobial agent, antibiotic agent, amino acid, peptide, vitamin, inorganic element, protein synthesis co-factor, hormone, endocrine tissue, synthesizer, enzyme, polymer-cell scaffolding agent with parenchymal cells, angiogenic drug, demineralized bone powder, collagen lattice, antigenic agent, cytoskeletal agent, **mesenchymal stem cells**, bone digester, antitumor agent, cellular attractant, fibronectin, growth hormone cellular attachment agent, immunosuppressant, nucleic acid, surface active agent, hydroxy apatite and penetration enhancer.

20. The osteogenic composition of claim 1 wherein the entangled particles are thoroughly mixed in the carrier.

L6 ANSWER 187 OF 191 USPATFULL on STN
94:26287 Shaped, swollen demineralized bone and its use in bone repair.
Prewett, Annamarie B., Little Silver, NJ, United States
Stikeleather, Roger C., Doylestown, PA, United States
Bogdansky, Simon, Marlboro, NJ, United States
O'Leary, Robert K., Spring Lake, NJ, United States
Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
US 5298254 19940329
APPLICATION: US 1991-809580 19911217 (7)
DOCUMENT TYPE: Utility; Granted.

AB A shaped piece of swollen demineralized bone which can also be plasticized is provided for use in surgical bone repair.

CLM What is claimed is:
1. A shaped piece of swollen demineralized bone having substantially

regular geometry and/or greater than 12 mm. in size along at least one dimension thereof, the bone being combined with a biocompatible swelling agent, wherein the swelling agent is selected from the group consisting of ethylene glycol, diethylene glycol, triethylene glycol, 1,2-propanediol, trimethylolethane, trimethylopropane, erythritol, pentaerythritol, polyethylene glycols, xylitol, sorbitol, mannitol, dulcitol, arabinose, xylose, ribose, adonitol, arabitol, rhamose, inositol, fructose, galactose, glucose, mannose, sorbose, sucrose, maltose, lactose, maltitol, lactitol, stachyose, maltopentaose, cyclomaltohexaose, carrageenan, agar, alginic acid, guar gum, gum tragacanth, locust bean gum, gum arabic, xanthan gum, amylose and mixtures thereof.

2. A shaped piece of a swollen demineralized bone having substantially regular geometry and/or greater than 12 mm. in size along at least one dimension thereof, the bone being combined with a biocompatible swelling agent, wherein the swelling agent is selected from a member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound ester, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound ester and mixtures thereof, and the polyhydroxy compound is selected from the group consisting of acyclic polyhydric alcohols, non-reducing sugars, sugar alcohols, sugar acids, monosaccharides, disaccharides, water-soluble or water dispersible oligosaccharides, polysaccharides, polyalkylene glycols and mixtures thereof.

3. The bone of claim 2 wherein the swelling agent is selected from the group consisting of glycerol, glycerol monoester and glycerol diester.

4. The bone of claim 2 wherein the swelling agent is selected from the group consisting of monosaccharide, monosaccharide ester, disaccharide, disaccharide ester, oligosaccharide, oligosaccharide ester and mixtures thereof.

5. The bone of claim 2 wherein the swelling agent is selected from the group consisting of fructose, glucose and mixtures thereof.

6. The bone of claim 2 wherein the swelling agent is a liquid solution of sucrose.

7. The bone of claim 2 wherein the swelling agent is an aqueous solution of sucrose.

8. The bone of claim 2 wherein the swelling agent is a liquid solution of a fatty acid monoester of glycerol.

9. The bone of claim 2 wherein the swelling agent is a fatty acid monoester dissolved in a solvent which is a different liquid polyhydroxy compound and/or ester thereof.

10. The bone of claim 2 wherein the swelling agent is a fatty acid monoester dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

11. The bone of claim 2 wherein the swelling agent is glycerol monolaurate dissolved in a solvent.

12. The bone of claim 2 wherein the swelling agent is glycerol monolaurate dissolved in a solvent which is a different liquid polyhydroxy compound and/or ester thereof.

13. The bone of claim 2 wherein the swelling agent is glyceryl monolaurate dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

14. The bone of claim 2 wherein the demineralized bone is derived from cortical bone, cancellous and/or corticocancellous autogenous, xenogeneic and/or allogeneic bone tissue.

15. The bone of claim 2 wherein the demineralized bone is derived from cortical allogeneic bone tissue.

16. The bone of claim 2 wherein a composition comprising said bone contains from about 5 to about 90 weight percent demineralized bone and from about 10 to about 95 weight percent swelling agent.

17. The bone of claim 2 wherein said composition contains from about 20 to about 80 weight percent demineralized bone and from about 20 to about 80 weight percent swelling agent.

18. The bone of claim 2 containing at least one additional ingredient selected from the group consisting of antiviral agent, antimicrobial agent, antibiotic agent, amino acid, magainin, peptide, vitamin, protein synthesis co-factor, hormone, endocrine tissue, synthesizer, enzyme, polymer-cell scaffolding agent with parenchymal cells, surface cell antigen eliminator, angiogenic drug, polymeric drug carrier, collagen lattice, antigenic agent, cytoskeletal agent, **mesenchymal stem cells**, bone digester, antitumor agent, cellular attractant, fibronectin, growth hormone cellular attachment agent, immunosuppressant, nucleic acid, surface active agent, hydroxyapatite and penetration enhancer.

19. The bone of claim 1 which is additionally plasticized before being applied to a bone defect site.

20. The bone of claim 19 wherein said demineralized osteogenic bone is plasticized with an aqueous composition.

21. The bone of claim 20 wherein said aqueous composition additionally includes at least one disinfectant selected from the group consisting of gentamicin sulfate, bacitracin, polymyxin B, neomycin and sodium cefazolin and mixtures thereof.

22. A shaped piece of swollen demineralized bone having substantially regular geometry and/or greater than 12 mm. in size along at least one dimension thereof, the bone being combined with a biocompatible swelling agent and in the form of a sheet, ring, disk, cube, cylinder or tube, wherein the biocompatible swelling agent is selected from the group consisting of acyclic polyhydric alcohols, non-reducing sugars, sugar alcohols, sugar acids, monosaccharides, disaccharides, water-soluble or water dispersible oligosaccharides, polysaccharides, polyalkylene glycols, known esters of any of the foregoing and mixtures thereof.

23. The bone of claim 22 which is in the form of a tubular screw stabilizer or sleeve, a substantially cylindrical bone plug, a pledget, a solid or hollow wedge, a ribbon or tape, a rope, a sheet of patch, a liner or a clip.

24. A method of preparing a shaped piece of osteogenic bone having substantially regular geometry and/or greater than 12 mm. in size along at least one dimension thereof, for application to a bone defect site to promote new bone growth at the site, comprising a) demineralizing bone tissue, and b) swelling the demineralized bone tissue by combining with a swelling agent selected from the group consisting of acyclic polyhydric alcohols, non-reducing sugars, sugar alcohols, sugar acids, monosaccharides, disaccharides, water-soluble or water dispersible oligosaccharides, polysaccharides, polyalkylene glycols, known esters of any of the foregoing and mixtures thereof.

25. The method of claim 24 wherein the swelling agent is selected from a

member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound ester, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound ester and mixtures thereof.

26. The method of claim 24 additionally comprising d) plasticizing the bone before application to the bone defect site.

27. The method of claim 26 wherein c) the bone is plasticized by contacting the demineralized, swollen bone with an aqueous composition.

28. The method of claim 26 wherein the piece of bone is shaped prior to demineralization, after demineralization and prior to swelling, or after plasticization.

29. The bone of claim 22 which is additionally plasticized before being applied to a bone defect site.

30. A shaped piece of swollen demineralized bone having substantially regular geometry and/or greater than 12 mm. in size along at least one dimension thereof, the bone being combined with a biocompatible swelling agent, wherein the swelling agent is selected from a member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound ester, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound ester and mixtures thereof, and the polyhydroxy compound possesses from 2 to about 18 carbon atoms and is selected from the group consisting of acyclic polyhydric alcohols, non-reducing sugars, sugar alcohols, sugar acids, monosaccharides, disaccharides, water-soluble or water dispersible oligosaccharides, polysaccharides, polyalkylene glycols and mixtures thereof.

L6 ANSWER 188 OF 191 USPATFULL on STN
94:17799 Flowable demineralized bone powder composition and its use in bone repair.
O'Leary, Robert K., Spring Lake, NJ, United States
McBrayer, Patrick A., Yardley, PA, United States
Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
US 5290558 19940301
APPLICATION: US 1990-573458 19900827 (7)
DOCUMENT TYPE: Utility; Granted.

AB A flowable demineralized bone powder composition is provided for use in surgical bone repair.

CLM What is claimed is:

1. A flowable composition for application to a bone defect site to promote new bone growth at the site which comprises a new bone growth-inducing amount of dimineralized osteogenic bone powder in a biocompatible carrier, the carrier being selected from a member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound ester, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound ester and mixtures thereof, wherein the carrier is on of the following components (i)-(iv); (i) the carrier is selected from the group consisting of glycerol, glycerol monoester and glycerol diester; (ii) the carrier is selected from the group consisting of monosaccharide, monosaccharide ester, disaccharide, disaccharide ester, oligosaccharide, oligosaccharide ester and mixture thereof; (iii) the carrier is a fatty acid monoester dissolved in a solvent which is a different liquid polyhydroxy compound and/or ester thereof; and (iv) the carrier is glycerol monolaurate dissolved in a solvent.

2. The composition of claim 1 containing at least one additional ingredient selected from at least one of bone morphogenic protein, transforming growth factor and insulin-like growth factor (IGF-1).

3. The composition of claim 1 wherein the carrier is one of the

following components (1) and (2): (1) the carrier is selected from the group consisting of fructose, glucose, sucrose and mixtures thereof; and (2) the carrier is glycerol monolaurate dissolved in a solvent which is a different liquid polyhydroxy compound and/or ester thereof.

4. A flowable composition for application to a bone defect site to promote new bone growth at the site which consists essentially of a new bone growth-inducing amount of demineralized osteogenic bone powder in a biocompatible carrier, the carrier being selected from a member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound ester, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound ester and mixtures thereof, wherein the polyhydroxy compound is selected from the group consisting of acyclic polyhydric alcohols, non-reducing sugars, sugar alcohols, sugar acids, monosaccharides, disaccharides, water-soluble or water dispersible oligosaccharides, polysaccharides, polyalkylene glycols and mixture thereof.

5. The composition of claim 4 containing at least one additional ingredient selected from the group consisting of antiviral agent, antimicrobial agent, antibiotic agent, amino acid, peptide, vitamin, protein synthesis co-factor, hormone, endocrine tissue, synthesizer, enzyme, polymer-cell scaffolding agent with parenchymal cells, angiogenic drug, polymeric drug carrier, antigenic agent, cytoskeletal agent, **mesenchymal stem cells**, bone digester, antitumor agent, cellular attractant, fibronectin, growth hormone cellular attachment agent, immunosuppressant, nucleic acid, surface active agent, hydroxy apatite and penetration enhancer.

6. The composition of claim 1 wherein the polyhydroxy compound is selected from the group consisting of ethylene glycol, diethylene glycol, triethylene glycol, 1,2-propanediol, trimethylolethane, trimethylopropane, erythritol, pentaerythritol, polyethylene glycols, xylitol, sorbitol, mannitol, dulcitol, arabinose, xylose, ribose, adonitol, arabitol, rhamose, inositol, fructose, galactose, glucose, mannose, sorbose, sucrose, maltose, lactose, maltitol, lactitol, stachyose, maltopentaose, cyclomaltohexaose, carrageenan, agar, alginic acid, guar gum, gum tragacanth, locust bean gum, gum arabic, xanthan gum, amylose and mixture thereof.

7. A flowable composition for application to a bone defect site to promote new bone growth at the site which comprises a new bone growth-inducing amount of demineralized osteogenic bone powder in a biocompatible carrier, the carrier being selected from a member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound ester, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound ester and mixtures thereof, wherein the carrier is one of the following components (i)-(vi): (i) the carrier is a liquid solution of sucrose; (ii) the carrier is a liquid solution of a fatty acid monoester of glycerol; (iii) the carrier is a fatty acid monoester dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof; (iv) the carrier is a flowable solution or paste of sucrose and glycerol; (v) the carrier is a flowable solution or paste of sucrose and polyethylene glycol; and (vi) the carrier is selected from the group consisting of fructose, dextrose and mixtures thereof.

8. The composition of claim 7 wherein the carrier is one of the following components (1) and (2): (1) the carrier is an aqueous solution of sucrose; and (2) the carrier is glycerol monolaurate dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

9. The composition of claim 8 wherein the carrier is glyceryl

monolaurate dissolved in glycerol or a 4:1 to 1:4 mixture of glycerol and propylene glycol.

10. A flowable composition for application to a bone defect site to promote new bone growth at the site which comprises a new bone growth-inducing amount of demineralized osteogenic bone powder in a biocompatible carrier, the carrier being selected from a member of the group consisting of liquid polyhydroxy compound, liquid polyhydroxy compound ester, liquid solution of solid polyhydroxy compound, liquid solution of solid polyhydroxy compound ester and mixtures thereof, wherein the polyhydroxy compound is selected from the group consisting of acyclic polyhydric alcohols, non-reducing sugars, sugar alcohols, sugar acids, monosaccharides, disaccharides, water-soluble or water dispersible oligosaccharides, polysaccharides, polyalkylene glycols and mixtures thereof.

11. The composition of claim 10 wherein the polyhydroxy compound is selected from the group consisting of ethylene glycol, diethylene glycol, triethylene glycol, 1,2-propanediol, trimethylolethane, trimethylopropane, erythritol, pentaerythritol, polyethylene glycols, xylitol, sorbitol, mannitol, dulcitol, arabinose, xylose, ribose, adonitol, arabitol, rhamose, inositol, fructose, galactose, glucose, mannose, sorbose, sucrose, maltose, lactose, maltitol, lactitol, stachyose, maltopentaose, cyclomaltohexaose, carrageenan, agar, alginic acid, guar gum, gum tragacanth, locust bean gum, gum arabic, xanthan gum, amylose and mixtures thereof.

12. The composition of claim 10 wherein said demineralized osteogenic bone powder has been subjected to acid demineralization treatment.

13. The composition of claim 10 wherein the average particle size of the demineralized bone powder is from about 0.1 to about 1.2 cm.

14. The composition of claim 10 wherein the average particle size of the demineralized bone powder is from about 0.2 to about 1 cm.

15. The composition of claim 10 wherein the demineralized bone powder is derived from cortical bone, cancellous and/or corticocancellous autogenous, xenogeneic and/or allogeneic bone tissue.

16. The composition of claim 10 containing from about 5 to about 90 weight percent demineralized bone powder and from about 10 to about 95 weight percent carrier.

17. The composition of claim 10 containing from about 20 to about 80 weight percent demineralized bone powder and from about 20 to about 80 weight percent carrier.

18. The composition of claim 10 containing at least one additional ingredient selected from the group consisting of antiviral agent, antimicrobial agent, antibiotic agent, amino acid, peptide, vitamin, protein synthesis co-factor, hormone, endocrine tissue, synthesizer, enzyme, polymer-cell scaffolding agent with parenchymal cells, angiogenic drug, polymeric drug carrier, collagen lattice, antigenic agent, cytoskeletal agent, **mesenchymal stem cells**, bone digester, antitumor agent, cellular attractant, fibronectin, growth hormone cellular attachment agent, immunosuppressant, nucleic acid, surface active agent, hydroxy apatite and penetration enhancer.

19. The composition of claim 10 containing a bioerodable polymer.

20. The composition of claim 10 additionally comprising a thickener selected from at least one of polyvinyl alcohol, polyvinylpyrrolidone, hydroxypropyl methylcellulose, carboxyl methylcellulose, pectin, food-grade texturizing agent, gelatin, dextran, collagen, starch, hydrolyzed polyacrylonitrile, hydrolyzed polyacrylamide and polyacrylic

acid salt.

21. The composition of claim 12 wherein said demineralized bone powder has additionally been subjected to defatting/disinfecting treatment.

L6 ANSWER 189 OF 191 USPATFULL on STN
94:11227 Swollen demineralized bone particles, flowable osteogenic composition containing same and use of the composition in the repair of osseous defects
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Bogdansky, Simon, Marlboro, NJ, United States
O'Leary, Robert K., Spring Lake, NJ, United States
Osteotech, Inc., Shrewsbury, NJ, United States (U.S. corporation)
US 5284655 19940208
APPLICATION: US 1992-830942 19920204 (7)
DOCUMENT TYPE: Utility; Granted.

AB Swollen demineralized bone particles are formulated into a flowable osteogenic composition which is useful in the repair of osseous defects.

CLM What is claimed is:

1. A flowable osteogenic composition which comprises from about 5 to about 90 weight percent swollen demineralized autogenous or allogenic bone particles exhibiting an average increase in volume and/or weight of at least about 10 percent following contact of the unswollen demineralized bone particles with a demineralized bone particle swelling agent and from about 10 to about 95 weight percent of a biocompatible fluid carrier selected from a member of the group consisting of liquid polyhydroxy compound, liquid ester of a polyhydroxy compound, liquid solution of a solid polyhydroxy compound, liquid solution of a solid ester of a polyhydroxy compound and mixtures thereof, wherein the polyhydroxy compound is selected from the group consisting of acyclic polyhydric alcohols, polyalkylene glycols, non-reducing sugars, sugar alcohols, sugar acids, monosaccharides, disaccharides, water-soluble or water dispersible oligosaccharides, polysaccharides and mixtures thereof.

2. The composition of claim 1 containing at least one additional component selected from the group consisting of antiviral agent, antimicrobial agent, antibiotic agent, amino acid, peptide, vitamin, protein synthesis co-factor, hormone, endocrine tissue, synthesizer, enzyme, polymer-cell scaffolding agent with parenchymal cells, angiogenic drug, collagen lattice, antigenic agent, cytoskeletal agent, **mesenchymal stem cells**, bone digester, antitumor agent, cellular attractant, fibronectin, growth hormone cellular attachment agent, immunosuppressant, nucleic acid, surface active agent, hydroxy apatite and penetraction enhancer.

3. The swollen demineralized bone particles of claim 1 exhibiting an average increase in volume and/or weight of at least about 20 percent following contact of the unswollen demineralized bone particles with the demineralized bone particle swelling agent.

4. The swollen demineralized bone particles of claim 1 exhibiting an average increase in volume and/or weight of at least about 30 percent following contact of the unswollen demineralized bone particles with the demineralized bone particle swelling agent.

5. The composition of claim 1 wherein the swollen demineralized bone particles have an average maximum dimension of from about 0.01 to about 10 mm.

6. The composition of claim 1 wherein the carrier is glyceryl monolaurate dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

7. The composition of claim 1 containing from about 20 to about 80

weight percent swollen demineralized bone particles and from about 20 to about 80 weight percent carrier.

8. The composition of claim 1 wherein the carrier is selected from the group consisting of glycerol, glycerol monoester and glycerol diester.

9. The composition of claim 1 wherein the carrier is selected from the group consisting of monosaccharide, monosaccharide ester, disaccharide, disaccharide ester, oligosaccharide, oligosaccharide ester and mixtures thereof.

10. The composition of claim 10 wherein the carrier is dextran.

11. A flowable osteogenic composition which comprises from about 5 to about 90 weight percent swollen demineralized autogenous or allogenic bone particles exhibiting an average increase in volume and/or weight of at least about 10 percent following contact of the unswollen demineralized bone particles with a demineralized bone particle swelling agent and from about 10 to about 95 weight percent of a biocompatible fluid carrier selected from a member of the group consisting of liquid polyhydroxy compound, liquid ester of a polyhydroxy compound, liquid solution of a solid polyhydroxy compound, liquid solution of a solid ester of a polyhydroxy compound and mixtures thereof, wherein the polyhydroxy compound is selected from the group consisting of ethylene glycol, diethylene glycol, triethylene glycol, 1,2-propanediol, glycerol, trimethylolethane, trimethylopropane, erythritol, pentaerythritol, polyethylene glycols, polyvinylalcohols, xylitol, sorbitol, mannitol, dulcitol, arabinose, xylose, ribose, adonitol, arabitol, rhamose, inositol, fructose, galactose, glucose, mannose, sorbose, sucrose, dextrose, maltose, lactose, maltitol, lactitol, stachyose, maltopentaose, eyclomaltohexaose, carrageenan, agar, dextran, alginic acid, guar gum, gum tragacanth, locust bean gum, gum arabic, xanthan gum, amylose and mixtures thereof.

12. The composition of claim 1 wherein the carrier is a liquid solution of sucrose.

13. The composition of claim 1 wherein the carrier is an aqueous solution of sucrose.

14. The composition of claim 1 wherein the carrier is a liquid solution of a fatty acid monoester of glycerol.

15. The composition of claim 1 wherein the carrier is a fatty acid monoester dissolved in a solvent which is a different liquid polyhydroxy compound and/or ester thereof.

16. A flowable osteogenic composition which comprises from about 5 to about 90 weight percent swollen demineralized autogenous or allogenic bone particles exhibiting an average increase in volume and/or weight of at least about 10 percent following contact of the unswollen demineralized bone particles with a demineralized bone particle swelling agent and from about 10 to about 95 weight percent of a biocompatible fluid carrier selected from a member of the group consisting of liquid polyhydroxy compound, liquid ester of a polyhydroxy compound, liquid solution of a solid polyhydroxy compound, liquid solution of a solid ester of a polyhydroxy compound and mixtures thereof, wherein the carrier is a fatty acid monoester dissolved in a solvent selected from the group consisting of propylene glycol, glycerol, monoacetin, diacetin, liquid polyethylene glycol and mixtures thereof.

17. The composition of claim 1 wherein the carrier is glycerol monolaurate dissolved in a solvent.

18. The composition of claim 1 wherein the carrier is glycerol monolaurate dissolved in a solvent which is a different liquid

polyhydroxy compound and/or ester thereof.

L6 ANSWER 190 OF 191 USPATFULL on STN
93:56458 Method for treating connective tissue disorders.
Caplan, Arnold I., 1300 Oakridge Dr., Cleveland Heights, OH, United States 44121
Haynesworth, Stephen E., 3643 Antisdale Rd., Cleveland Heights, OH, United States 44118
US 5226914 19930713
APPLICATION: US 1990-614912 19901116 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to various processes and devices for utilizing isolated and culturally expanded marrow-derived mesenchymal cells (i.e. mesenchymal stem cells) for treating skeletal and other connective tissue disorders.
CLM What is claimed is:
1. A method for repairing connective tissue damage comprising: a) providing culturally expanded purified human marrow-derived mesenchymal cells which have been isolated from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate **mesenchymal stem cell** growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; and, b) applying the culturally expanded purified human marrow-derived mesenchymal cells to an area of connective tissue damage under conditions suitable for differentiating the cells into connective tissue cells necessary for repair.

2. The method of claim 1 wherein the culturally expanded purified marrow-derived mesenchymal cells are applied to the area of connective tissue damage by in vivo administration.

3. The method of claim 1 wherein the culturally expanded purified marrow-derived mesenchymal cells are applied to the area of connective tissue damage by injection.

4. The method of claim 1, further comprising the step of adding to said **mesenchymal stem cells** a factor which stimulates differentiation of the marrow-derived mesenchymal cells into osteocytes.

5. A method for enhancing implantation of a prosthetic device in connective tissue comprising: a) providing culturally expanded purified human marrow-derived mesenchymal cells which have been isolated from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate **mesenchymal stem cell** growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; b) adhering said culturally expanded purified human marrow-derived mesenchymal cells on to a prosthetic device; and, c) implanting the prosthetic device containing the culturally expanded purified marrow-derived mesenchymal cells under conditions suitable for differentiating the cells into connective tissue.

6. The method of claim 5 further comprising the steps of adding to said marrow-derived mesenchymal cells a factor which stimulates differentiation of the marrow-derived mesenchymal cells into osteocytes.

7. A method for repairing connective tissue damage comprising the steps of: a) providing a bone marrow specimen containing human **mesenchymal stem cells** and bone pieces; b) adding the bone marrow specimen to a medium which contains factors which stimulate **mesenchymal stem cell** growth without differentiation and allows, when cultured, for the selective adherence of only the **mesenchymal stem cells** to a substrate surface; c) separating the bone pieces from the bone marrow medium mixture; d) dissociating the marrow cells into single cells; e)

culturing the dissociated marrow cells in the bone marrow medium mixture; f) separating the non-adherent matter from the substrate surface thereby producing isolated culturally expanded **mesenchymal stem cells**; and, g) applying the culturally expanded purified **mesenchymal stem cells** to the area of connective tissue damage under conditions suitable for differentiating the cells into the type of connective tissue cells necessary for repair.

8. The method of claim 7 wherein the culturally expanded purified **mesenchymal stem cells** are applied to the area of connective tissue damage by in vivo administration.

9. The method of claim 7 wherein the culturally expanded purified **mesenchymal stem cells** are applied to the area of connective tissue damage by injection.

10. The method of claim 7 further comprising the step of adding to said **mesenchymal stem cells** a factor which stimulates differentiation of the **mesenchymal stem cells** into osteocytes.

11. The method of claim 7 wherein said medium is comprised of BGJ_b medium with 10% fetal bovine serum.

12. The method of claim 7 wherein said medium is comprised of F-12 nutrient mixture.

13. A method for enhancing implantation of a prosthetic device in a connective tissue comprising: a) providing a bone marrow specimen containing human **mesenchymal stem cells** and bone pieces; b) adding the bone marrow specimen to a medium which contains factors which stimulate **mesenchymal stem cell** growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; c) separating the bone pieces from the bone marrow medium mixture; d) dissociating the marrow cells into single cells; e) culturing the dissociated marrow cells in the bone marrow medium mixture; f) separating non-adherent matter from the substrate surface thereby producing isolated culturally expanded **mesenchymal stem cells**; g) adhering said culturally expanded purified **mesenchymal stem cells** on to a prosthetic device; and, h) implanting the prosthetic device containing the culturally expanded purified **mesenchymal stem cells** under conditions suitable for differentiating the cells into skeletal tissue.

14. The method of claim 13, further comprising the steps of adding to said **mesenchymal stem cells** a factor which stimulates differentiation of the **mesenchymal stem cells** into osteocytes.

15. The method of claim 13, wherein said medium is comprised of BGJ_b medium with 10% fetal bovine serum.

16. The method of claim 13, wherein said medium is comprised of F-12 nutrient mixture.

17. A method for generating a hematopoietic **stem cell** reserve comprising: a) providing human marrow-derived **mesenchymal stem cells** that have been isolated, purified and culturally expanded; b) applying the isolated, purified and culturally expanded marrow-derived human **mesenchymal stem cells** to a porous carrier; c) implanting the porous carrier containing the **mesenchymal stem cells** into a host patient; d) allowing for a sufficient period of time for inducement of hematopoietic **stem cells** present in the host patient into the porous carrier; and e) harvesting the hematopoietic **stem cells** present in the porous carrier.

18. The method of claim 17, wherein said porous carrier comprises about 60% hydroxyapatite and about 40% tricalcium phosphate.

19. A method for generating a human hematopoietic **stem cell** reserve comprising: a) providing a bone marrow specimen containing human marrow-derived **mesenchymal stem cells** and bone pieces; b) adding the bone marrow specimen to a medium which contains factors which stimulate the human marrow-derived **mesenchymal stem cells** to grow without differentiation and allows, when cultured, for selective adherence of only the marrow-derived human **mesenchymal stem cells** to a substrate surface; c) separating the bone pieces from the bone marrow medium mixture; d) dissociating the marrow cells into single cells; e) culturing the dissociated marrow cells in the bone marrow medium mixture; f) separating non-adherent matter from the substrate surface, thereby producing isolated culturally expanded human marrow-derived **mesenchymal stem cells**; g) applying the culturally expanded human marrow-derived **mesenchymal stem cells** to a porous carrier; h) implanting the porous carrier containing the culturally expanded marrow-derived mesenchymal cells into a host patient; i) allowing for a sufficient period of time for inducement of hematopoietic **stem cells** present in the host patient into the porous carrier; and, j) harvesting the hematopoietic **stem cells** collected by the porous carrier.

20. The method of claim 19, wherein said porous carrier is comprised of about 60% hydroxyapatite and about 40% tricalcium phosphate.

21. The method of claim 19, wherein said medium is comprised of BGJ_b Medium with 10% fetal bovine serum.

22. The method of claim 19, wherein said medium is comprised of F-12 Nutrient Mixture.

23. A method for repairing connective tissue damage comprising: a) providing a bone marrow specimen containing human **mesenchymal stem cells**; b) adding the bone marrow specimen to a medium thereby producing a bone marrow specimen-medium mixture, wherein said medium contains factors that stimulate **mesenchymal stem cell** growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; c) adding the bone marrow specimen-medium mixture to a density gradient which separates cells into low, medium and high density cell fractions based on differences in density; d) removing the low density cell fraction from the density gradient; e) adding the low density cell fraction to the medium used in step (b) to produce a low density cell fraction-medium mixture; f) culturing the low density cell fraction-medium mixture, thereby selectively adhering only the **mesenchymal stem cells** to the substrate surface; g) removing any non-adherent matter from substrate surface; h) removing the remaining adherent **mesenchymal stem cells** from the substrate surface with a releasing agent, thereby allowing for the isolated **mesenchymal stem cells** to be recovered; and, i) applying an culturally expanded purified human marrow-derived mesenchymal cells to the area of connective tissue damage under conditions suitable for differentiating the cells into connective tissue necessary for repair.

L6 ANSWER 191 OF 191 USPATFULL on STN
93:24463 Method for enhancing the implantation and differentiation of marrow-derived mesenchymal cells.
Caplan, Arnold I., 1300 Oakridge Dr., Cleveland Heights, OH, United States 44121
Haynesworth, Stephen E., 3643 Antisdale Rd., Cleveland Heights, OH, United States 44118
US 5197985 19930330
APPLICATION: US 1990-614915 19901116 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a method and device for enhancing the implantation and differentiation of marrow-derived mesenchymal cells (i.e. mesenchymal stem cells). The method and device of the invention are an effective means for treating skeletal and other connective tissue disorders.

CLM What is claimed is:

1. A method for inducing human marrow-derived **mesenchymal stem cells** to differentiate into bone-forming cells, comprising: a) providing human marrow-derived **mesenchymal stem cells** that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; b) applying the isolated, purified and culturally expanded human marrow-derived **mesenchymal stem cells** to a porous carrier; and, c) implanting the porous carrier containing the culturally expanded human marrow-derived **mesenchymal stem cells** into an environment containing factors necessary for differentiating the human **mesenchymal stem cells** into bone cells.

2. The method of claim 1, wherein said environment is in vivo.

3. The method of claim 1, wherein said porous carrier comprises about 60% hydroxyapatite and about 40% tricalcium phosphate.

4. A method for repairing skeletal defects comprising: a) providing marrow-derived human **mesenchymal stem cells** that have been culturally expanded from isolated and purified human marrow-derived **mesenchymal stem cells** which have been isolated from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; b) applying the culturally expanded marrow-derived human **mesenchymal stem cells** to a porous carrier; and, c) implanting the porous carrier containing the culturally expanded purified human marrow-derived **mesenchymal stem cells** into the defective skeletal tissue.

5. The method of claim 4, wherein said porous carrier is comprised of about 60% hydroxyapatite and about 40% tricalcium phosphate.

6. A method for repairing skeletal defects comprising: a) providing a bone marrow specimen containing human marrow-derived **mesenchymal stem cells** and bone pieces; b) adding the bone marrow specimen to a medium thereby producing a bone marrow specimen-medium mixture, wherein said medium contains factors which stimulate human marrow-derived **mesenchymal stem cell** growth without differentiation and allows, when cultured, for selective adherence of only the human marrow-derived **mesenchymal stem cells** to a substrate surface; c) separating the bone pieces from the bone marrow medium mixture; d) dissociating marrow cells in the bone marrow specimen-medium mixture into single cells; e) culturing the dissociated marrow cells in the bone marrow specimen-medium mixture thereby selectively adhering only the human **mesenchymal stem cells** to the substrate surface; f) separating non-adherent matter from the substrate surface, thereby producing isolated culturally expanded human **mesenchymal stem cells**; g) removing remaining adherent isolated and culturally expanded human **mesenchymal stem cells** from the substrate surface with a releasing agent; h) applying the isolated and culturally expanded human marrow-derived **mesenchymal stem cells** to a porous carrier comprised of about 60% hydroxyapatite and about 40% tricalcium phosphate; and, i) implanting the porous carrier containing the culturally expanded human marrow-derived **mesenchymal stem cells** into the defective skeletal tissue.

7. The method of claim 6, wherein said porous carrier is comprised of about 60% hydroxyapatite and about 40% tricalcium phosphate.

8. The method of claim 6, wherein said medium is comprised of BGJ_b Medium with 10% fetal bovine serum.

9. The method of claim 6, wherein said medium is comprised of F-12 Nutrient Mixture.

10. A method for inducing marrow-derived human **mesenchymal stem cells** to differentiate into cartilage-forming cells, comprising: a) providing human marrow-derived **mesenchymal stem cells** that have been culturally expanded from isolated and purified human marrow-derived **mesenchymal stem cells** which have been isolated from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; b) applying the culturally expanded human marrow-derived **mesenchymal stem cells** to a carrier formatted to promote round cell morphology; c) implanting the carrier containing the culturally expanded human marrow-derived **mesenchymal stem cells** into an environment containing factors necessary for differentiating the human **mesenchymal stem cells** into cartilage-forming cells.

11. A method for repairing damaged articular cartilage comprising: a) providing human marrow-derived **mesenchymal stem cells** that have been culturally expanded from isolated and purified human marrow-derived **mesenchymal stem cells** which have been isolated from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; b) applying the culturally expanded human marrow-derived **mesenchymal stem cells** to a carrier formatted to promote round cell morphology; and, c) implanting the carrier containing the culturally expanded human marrow-derived **mesenchymal stem cells** into the damaged articular cartilage.

12. A method for repairing damaged articular cartilage comprising: a) providing a bone marrow specimen containing human **mesenchymal stem cells** and bone pieces; b) adding the bone marrow specimen to a medium thereby producing a bone marrow specimen-medium mixture, wherein said medium contains factors which stimulate human marrow-derived **mesenchymal stem cell** growth without differentiation and allows, when cultured, for selective adherence of only the human marrow-derived **mesenchymal stem cells** to a substrate surface; c) separating the bone pieces from the bone marrow specimen-medium mixture; d) dissociating marrow cells in the bone marrow specimen-medium mixture into single cells; e) culturing the dissociated marrow cells in the bone marrow medium specimen-mixture thereby selectively adhering only the human **mesenchymal stem cells** to the substrate surface; f) separating non-adherent matter from the substrate surface, thereby producing isolated culturally expanded human marrow-derived **mesenchymal stem cells**; g) removing remaining adherent isolated culturally expanded human **mesenchymal stem cells** from the substrate surface with a releasing agent; h) applying the isolated culturally expanded human marrow-derived mesenchymal cells to a carrier formatted to promote round cell morphology; and, i) implanting the carrier containing the culturally expanded human marrow-derived mesenchymal cells into the damaged articular cartilage.

13. The method of claim 12, wherein said medium is comprised of BGJ_b Medium with 10% fetal bovine serum.

14. The method of claim 12, wherein said medium is comprised of F-12 Nutrient Mixture.

15. A method for repairing skeletal defects comprising: a) providing a bone marrow specimen containing human **mesenchymal stem cells**; b) adding the bone marrow specimen to a medium thereby producing a bone marrow specimen-medium mixture, wherein said medium contains factors that stimulate **mesenchymal stem cell** growth without differentiation and allows, when cultured, for selective adherence of only the **mesenchymal stem cells** to a substrate surface; c) adding the bone marrow specimen-medium mixture to a density gradient which separates cells into low, medium and high density cell fractions based on differences in density; d) removing the low density cell fraction from the density gradient; e) adding the low density cell fraction to the medium used in step (b) to produce a low density cell fraction-medium mixture; f) culturing the low density cell fraction-medium mixture, thereby selectively adhering only the **mesenchymal stem cells** to the substrate surface; g) removing any non-adherent matter from the substrate surface; h) removing remaining adherent **mesenchymal stem cells** from the substrate surface with a releasing agent, thereby allowing for the isolated **mesenchymal stem cells** to be recovered; i) applying the recovered isolated **mesenchymal stem cells** to a porous carrier comprised of about 60% hydroxyapatite and about 40% tricalcium phosphate; and, j) implanting the porous carrier containing the culturally expanded human marrow-derived **mesenchymal stem cells** into the skeletal defect.

=> d his

(FILE 'HOME' ENTERED AT 18:32:09 ON 19 FEB 2004)

FILE 'WPIDS' ENTERED AT 18:43:10 ON 19 FEB 2004
E LENHARD J M/IN
L1 8 S E3
L2 2037 S (LIPODYSTROPHY OR DYSLIPIDEMIA OR HYPERLIPIDEMIA OR FAT REDIS
L3 175 S L2 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L4 3 S L3 AND (HAART OR HIGHLY ACTIVE ANTIRETROVIRAL THERAPY)

FILE 'USPATFULL' ENTERED AT 18:50:28 ON 19 FEB 2004
L5 2263 S (STEM CELL?/CLM)
L6 191 S L5 AND (MESENCHYMAL STEM CELL?/CLM)

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	44.35	93.10

FILE 'MEDLINE' ENTERED AT 18:55:49 ON 19 FEB 2004

FILE LAST UPDATED: 19 FEB 2004 (20040219/UP). FILE COVERS 1958 TO DATE.

On December 14, 2003, the 2004 MeSH terms were loaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s mesenchymal stem cell?
15059 MESENCHYMAL
120687 STEM
2447293 CELL?

L7 735 MESENCHYMAL STEM CELL?
(MESENCHYMAL(W)STEM(W)CELL?)

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MISSING OPERATOR L7 AN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l7 and adipocyte?
12339 ADIPOCYTE?
L8 118 L7 AND ADIPOCYTE?

=> d l8,cbib,ab,110-118

L8 ANSWER 110 OF 118 MEDLINE on STN
91051811 Document Number: 91051811. PubMed ID: 2240160. Metaplastic change in **mesenchymal stem cells** induced by activated ras oncogene. Tzen C Y; Filipak M; Scott R E. (Department of Pathology, University of Tennessee Health Science Center, Memphis 38163.) AMERICAN JOURNAL OF PATHOLOGY, (1990 Nov) 137 (5) 1091-102. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.
AB 3T3 T murine **mesenchymal stem cells** have the potential to differentiate into a variety of different cell types even though they show a predilection to undergo **adipocyte** differentiation in vitro. The possibility that the activated c-Ha-ras (EJras) oncogene might influence the pathway of differentiation of these stem cells is investigated in the current study. Activated ras oncogene was transfected and stably expressed in 3T3 T cells; assays then were performed to determine its effect on differentiation. The results show that all EJras-transfected cell lines lose their ability to differentiate to **adipocytes** and instead differentiate into cells that express many characteristics of macrophages. Such cells contain numerous cytoplasmic granules, extensive nonspecific esterase activity, and anchorage-independent growth. The modulation of differentiation pathway from an **adipocyte** lineage to a macrophagelike cell lineage does not result from the transforming effect of EJras, because a nontransformed cell clone that expresses p21EJras protein also exhibits this modified differentiation pathway. These data suggest that the EJras oncogene specifically modulates the differentiation pathway of 3T3 T **mesenchymal stem cells**. This experimental system should therefore provide an excellent model to evaluate the mechanistic role of EJras in the process of metaplasia.

L8 ANSWER 111 OF 118 MEDLINE on STN
89351499 Document Number: 89351499. PubMed ID: 3076440. Aproliferin: a modulator of proliferative potential. Wier M L; Scott R E. (Electro-Nucleonics, Columbia, MD 21046.) BIOFACTORS, (1988 Jul) 1 (2) 129-31. Ref: 28. Journal code: 8807441. ISSN: 0951-6433. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Cellular differentiation proceeds through a series of steps in which cells undergo modifications in cellular phenotype and proliferative potential. Differentiation has been extensively studied in 3T3-T **mesenchymal stem cells** and growth arrest, non-terminal and terminal differentiation have been identified as three distinct stages in the **adipocyte** differentiation of these cells. The terminal stage of differentiation is associated with irreversible loss of proliferative potential and commitment to the expression of the **adipocyte** phenotype. A protein has been partially purified from human plasma that can induce the transition of 3T3-T **adipocytes** from the non-terminal to the terminal state of differentiation. This protein, designated aproliferin, has a mol. wt of approximately 45,000 and is trypsin, acid and heat labile. Induction of terminal differentiation by aproliferin is associated with changes in the synthesis of a limited number of cellular proteins. The ability of aproliferin to induce terminal differentiation in non-terminally differentiated cells is highly specific as a wide variety of pharmacological and biochemical agents do not mimic the effects of this agent. Apoliferin may be one of an emerging class of molecules which can

affect differentiation and induce irreversible changes in cell function.

L8 ANSWER 112 OF 118 MEDLINE on STN

89170554 Document Number: 89170554. PubMed ID: 2647473. Integrated control of proliferation and differentiation of **mesenchymal stem cells**. Filipak M; Estervig D N; Tzen C Y; Minoo P; Hoerl B J; Maercklein P B; Zschunke M A; Edens M; Scott R E. (Section of Experimental Pathology, Mayo Clinic/Foundation, Rochester, MN 55905.) ENVIRONMENTAL HEALTH PERSPECTIVES, (1989 Mar) 80 117-25. Ref: 54. Journal code: 0330411. ISSN: 0091-6765. Pub. country: United States. Language: English.

AB The physiological control of cellular proliferation and differentiation is an integrated regulatory process. This conclusion is based upon observations using numerous in vivo and in vitro experimental systems of which murine BALB/c 3T3 T **mesenchymal stem cells** represent an excellent in vitro model. In these cells the coupling of growth arrest and differentiation occurs at a distinct biological state, and this predifferentiation arrest state is distinguishable by a variety of criteria from other restriction points, such as the growth factor deficiency arrest state and the nutrient deficiency arrest state. Most importantly, only cells at this predifferentiation arrest state acquire the potential to differentiate without undergoing DNA synthesis. From this state, differentiation can then occur as a two-step process. Cells first undergo nonterminal differentiation and, second, they terminally differentiate. Nonterminal differentiation is characterized by expression of a completely differentiated **adipocyte** phenotype with retention of proliferative potential. Thereafter, when nonterminally differentiated cells undergo the terminal event in differentiation, they irreversibly lose their proliferative potential. In this paper, data are reviewed which establish that the integrated control of proliferation and differentiation in 3T3 T **mesenchymal stem cells** is mediated both at the predifferentiation arrest state and at the state of nonterminal differentiation.

L8 ANSWER 113 OF 118 MEDLINE on STN

88257214 Document Number: 88257214. PubMed ID: 3384856. Differentiation of muscle, fat, cartilage, and bone from progenitor cells present in a bone-derived clonal cell population: effect of dexamethasone. Grigoriadis A E; Heersche J N; Aubin J E. (Medical Research Council Group in Periodontal Physiology, University of Toronto, Ontario, Canada.) JOURNAL OF CELL BIOLOGY, (1988 Jun) 106 (6) 2139-51. Journal code: 0375356. ISSN: 0021-9525. Pub. country: United States. Language: English.

AB RCJ 3.1, a clonally derived cell population isolated from 21-d fetal rat calvaria, expresses the osteoblast-associated characteristics of polygonal morphology, a cAMP response to parathyroid hormone, synthesis of predominantly type I collagen, and the presence of 1,25-dihydroxyvitamin D3-regulated alkaline phosphatase activity. When cultured in the presence of ascorbic acid, sodium beta-glycerophosphate, and the synthetic glucocorticoid dexamethasone, this clone differentiated in a time-dependent manner into four morphologically distinct phenotypes of known mesenchymal origin. Multinucleated muscle cells were observed as early as 9-10 d in culture, lipid-containing **adipocytes** formed after 12 d, chondrocyte nodules were observed after 16 d, and mineralized bone nodules formed after 21 d in culture. The differentiated cell types were characterized morphologically, histochemically, and immunohistochemically. The formation of **adipocytes** and chondrocytes was dependent upon the addition of dexamethasone; the muscle and bone phenotypes were also expressed at low frequency in the absence of dexamethasone. The sex steroid hormones progesterone and 17 beta-estradiol had no effect on differentiation in this system, suggesting that the effects of dexamethasone represent effects specific for glucocorticosteroids. Increasing concentrations of dexamethasone (10(-9)-10(-6) M) increased the numbers of myotubes, **adipocytes**, and chondrocytes; however, when present continuously for 35 d, the lower concentrations appeared to better maintain the muscle and **adipocyte** phenotypes. Bone nodules were not quantitated because the frequency of bone nodule formation was too low. Single cells obtained by plating RCJ 3.1 cells at limiting dilutions in

the presence of dexamethasone, were shown to give rise to subclones that could differentiate into either single or multiple phenotypes. Thus, the data suggest that this clonal cell line contains subpopulations of mesenchymal progenitor cells which can, under the influence of glucocorticoid hormones, differentiate in vitro into four distinct cell types. It is, therefore, a unique cell line which will be of great use in the study of the regulation of **mesenchymal stem cell** differentiation.

L8 ANSWER 114 OF 118 MEDLINE on STN

88012305 Document Number: 88012305. PubMed ID: 3309457. Adipose tissue development: the role of precursor cells and adipogenic factors. Part II: The regulation of the adipogenic conversion by hormones and serum factors. Loffler G; Hauner H. (Institut fur Biochemie, Mikrobiologie und Genetik der Universitat Regensburg.) KLINISCHE WOCHENSCHRIFT, (1987 Sep 1) 65 (17) 812-7. Ref: 142. Journal code: 2985205R. ISSN: 0023-2173. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB Cell culture systems have proven to be valuable models for the study of the processes involved in the formation of new fat cells. Two separate steps may be distinguished in **adipocyte** development. First, the determination of a **mesenchymal stem cell** into a preadipocyte, second, its conversion into a mature fat cell. In cloned cell lines adipose conversion depends on at least one postconfluent mitosis possibly induced by insulin-like growth factors or by as yet unknown mitogens. In addition growth hormone, glucocorticoids, and insulin are needed for conversion to take place. The adipose conversion of preadipocytes originating from the stromal vascular fraction of adipose tissue does not depend on postconfluent mitoses and needs only insulin and glucocorticoid hormones in physiological concentrations. However, the ability to undergo adipose conversion is not stable in these cells, but gets lost after repeated subcultures or seeding at low densities. In addition to stimulating hormones an increasing number of factors inhibiting the conversion process have also been detected, the physiological function of which remains unclear at the moment.

L8 ANSWER 115 OF 118 MEDLINE on STN

87002118 Document Number: 87002118. PubMed ID: 3756880. Differentiation, dedifferentiation, and transdifferentiation of BALB/c 3T3 T **mesenchymal stem cells**: potential significance in metaplasia and neoplasia. Sparks R L; Seibel-Ross E I; Wier M L; Scott R E. CANCER RESEARCH, (1986 Oct) 46 (10) 5312-9. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The expression of defects in the control of cellular differentiation is thought to be of etiological significance in the early stages of carcinogenesis. This possibility is supported by a variety of experimental studies including those that have established that metaplastic changes in cells can represent preneoplastic lesions in vivo. To evaluate this question in greater detail, we have used 3T3 T **mesenchymal stem cells** as a model system. These cells express certain characteristics of preneoplastic cells even though they can regulate their proliferation and even though they can undergo nonterminal and terminal differentiation into **adipocytes**. For example, they are immortal and aneuploid, and they show a proclivity to undergo spontaneous or induced neoplastic transformation compared to normal human cells. The question we sought to answer in the current experiments concerns whether predifferentiation growth arrest and/or nonterminal differentiation in such preneoplastic cells is completely reversible or whether these processes induce the expression of the new stable program that limits the cells' proliferative potential and reduces the cells' subsequent differentiation potential in a manner comparable to that which is thought to occur in normal stem cells. The results show that arrest at both the predifferentiation state and at the nonterminal differentiation state is a completely reversible phenomenon that does not limit the cells' subsequent growth or differentiation potential. In fact, the results show that, when nonterminally differentiated 3T3 T **adipocytes** are induced to dedifferentiate, they can subsequently redifferentiate into macrophages. We therefore suggest that preneoplasia as expressed in 3T3 T **mesenchymal**

stem cells is associated with the expression of defects in the ability to integrally control cellular differentiation and proliferation. As a result, the data suggest that such cells express an increased proclivity to undergo metaplastic change and complete neoplastic transformation.

L8 ANSWER 116 OF 118 MEDLINE on STN

86247904 Document Number: 86247904. PubMed ID: 3459667. Transforming growth factor type beta is a specific inhibitor of 3T3 T **mesenchymal stem cell** differentiation. Sparks R L; Scott R E. EXPERIMENTAL CELL RESEARCH, (1986 Aug) 165 (2) 345-52. Journal code: 0373226. ISSN: 0014-4827. Pub. country: United States. Language: English.

AB In the current studies we examined the effects of transforming growth factor type beta (TGF-beta) on the control of differentiation of BALB/c 3T3 T stem cells. We report that TGF-beta is a potent, reversible inhibitor of **adipocyte** differentiation (50% inhibition at approximately 0.06-0.08 ng/ml), while other biologically active polypeptides, such as epidermal growth factor (EGF), human growth hormone (hGH), and somatomedin C, have no specific effect on differentiation at even higher concentrations (200 ng/ml). We also report that TGF-beta inhibits differentiation in a cell cycle-dependent manner by its effect on a specific phase in the differentiation process. We therefore suggest that if TGF-beta is an important regulatory factor, one of its critical mechanisms of action may be its ability to inhibit the process of cell differentiation.

L8 ANSWER 117 OF 118 MEDLINE on STN

86196269 Document Number: 86196269. PubMed ID: 2422182. Regulation of the terminal event in cellular differentiation: biological mechanisms of the loss of proliferative potential. Wier M L; Scott R E. JOURNAL OF CELL BIOLOGY, (1986 May) 102 (5) 1955-64. Journal code: 0375356. ISSN: 0021-9525. Pub. country: United States. Language: English.

AB Human plasma has been demonstrated to contain factors that induce the sequential expression of nonterminal and terminal **adipocyte** differentiation in 3T3 T **mesenchymal stem cells**. We now report the development of methods for the isolation of purified populations of nonterminally differentiated cells and terminally differentiated cells, and we show that it is possible to experimentally induce transition from the nonterminal to the terminal state of differentiation. With this model system it is therefore now possible to examine the biological and molecular processes associated with the terminal event in differentiation, i.e., the irreversible loss of proliferative potential. In this regard, we demonstrate that transition from the nonterminal to terminal state of differentiation is a complex metabolic process that consists of at least two steps and that this process can be triggered by pulse exposure to an inducer for approximately 12 h but that approximately 24-48 h is required for the process to be completed. The data also establish that induction of the terminal event in differentiation requires protein synthesis but not RNA and DNA synthesis. These and additional results suggest that loss of proliferative potential associated with the terminal event in cellular differentiation is a distinct regulatory process, and we suggest that defects in this regulatory process may be of etiological significance in the pathogenesis of specific human diseases, especially cancer.

L8 ANSWER 118 OF 118 MEDLINE on STN

82197518 Document Number: 82197518. PubMed ID: 6176995. Pre-**adipocyte** determination either by insulin or by 5-azacytidine. Sager R; Kovac P. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1982 Jan) 79 (2) 480-4. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB CHEF/18 is a diploid Chinese hamster cell line of embryonic origin, which is fibroblastic in structure, but behaves like a **mesenchymal stem cell** line in its ability to differentiate into **adipocytes**, myoblasts, and chondrocytes. With these cells, **adipocyte** formation has been divided experimentally into two stages: (i) determination of pre-**adipocytes**, which have lost the ability to form other cell types while retaining their fibroblast structure; and (ii) commitment or

terminal differentiation, in which lipids accumulate, **adipocyte** structure develops, and cells lose the ability to divide. This paper reports that the first stage can be induced by exposure to 5-azacytidine or 2'-deoxy-5-azacytidine, drugs that also induce CHEF cells to form other mesenchymal cell types, or by growth with added insulin. Pre-**adipocytes** are distinguished from CHEF stem cells by (i) their inability to form other mesenchymal cell types; and (ii) their rapid accumulation of lipid in response to added insulin. The possibility is discussed that both insulin and the cytidine analogs promote differentiation by the same mechanism, namely changes in the pattern of DNA methylation.

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(FILE 'HOME' ENTERED AT 18:32:09 ON 19 FEB 2004)

FILE 'WPIDS' ENTERED AT 18:43:10 ON 19 FEB 2004
E LENHARD J M/IN
L1 8 S E3
L2 2037 S (LIPODYSTROPHY OR DYSLIPIDEMIA OR HYPERLIPIDEMIA OR FAT REDIS
L3 175 S L2 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L4 3 S L3 AND (HAART OR HIGHLY ACTIVE ANTIRETROVIRAL THERAPY)

FILE 'USPATFULL' ENTERED AT 18:50:28 ON 19 FEB 2004
L5 2263 S (STEM CELL?/CLM)
L6 191 S L5 AND (MESENCHYMAL STEM CELL?/CLM)

FILE 'MEDLINE' ENTERED AT 18:55:49 ON 19 FEB 2004
L7 735 S MESENCHYMAL STEM CELL?
L8 118 S L7 AND ADIPOCYTE?

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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 19:00:06 ON 19 FEB 2004